Washington State Health Care Authority

Health Technology Assessment

Cardiac Nuclear Imaging

Final Evidence Report: Appendices

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CARDIAC NUCLEAR IMAGING

APPENDICES A - F

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APPENDIX A

Quality Assessment of diagnostic accuracy studies: QUADAS-2

QUADAS-2 tool for assessing the quality of diagnostic accuracy studies consists of 4 domains: 1) patient selection; 2) index test; 3) reference standard; and 4) flow and timing. Each domain is graded based on risk of bias and applicability. Signaling questions help to aid judgment for risk of bias in each domain.

Domain 1: Patient Selection

Risk of Bias: Could the selection of patients have introduced bias?
Signaling question 1: Was a consecutive or random sample of patients enrolled?
Signaling question 2: Was a case–control design avoided?
Signaling question 3: Did the study avoid inappropriate exclusions?

Applicability: Are there concerns that the included patients and setting do not match the review question?

Domain 2: Index Test

Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?
Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?
Signaling question 2: If a threshold was used, was it pre specified?

Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Domain 3: Reference Standard

Risk of Bias: could the reference standard, its conduct, or its interpretation have introduced bias?
Signaling question 1: Is the reference standard likely to correctly classify the target condition?
Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?

Domain 4: Flow and Timing

Risk of Bias: Could the patient flow have introduced bias?
Signaling question 1: Was there an appropriate interval between the index test and reference standard?
Signaling question 2: Did all patients receive the same reference standard?
Signaling question 3: Were all patients included in the analysis?

(No Applicability question for domain 4.)

Answering a 'no' for any signaling questions indicates a potential for bias.
Answering 'yes' to all the questions indicates low risk of bias.
In case of insufficient information provided in the study, 'unclear' category can be used.

Applicability questions can also be graded as 'low,' 'high' or 'unclear.'

QUADAS-2 does not generate a 'summary-score;' instead, a tabular representation helps summarize the quality for each domain.

Source: Whiting PF et al. *Ann Intern Med*. 2011;155(8):529-536.

APPENDIX B

Search Strategy for Medline

Databases searched:

- Medline 1996 to Present with Daily Update
- EBM Reviews – Cochrane Central Register of Controlled Trials, February 2013
- EBM Reviews – Database of Abstracts of Reviews of Effects, 1st Quarter 2013

1. exp Tomography, Emission-Computed/
2. Radiopharmaceuticals/
3. 1 or 2
4. Coronary Disease/
5. Coronary Artery Disease/
6. Coronary disease/
7. Coronary artery disease/
8. Coronary occlusion/
9. Coronary stenosis/
10. Coronary restenosis/
11. Coronary thrombosis/
12. Coronary vasospasm/
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13
15. Prognosis/ or
16. Treatment outcome/ OR
17. Follow-up studies/ or
18. Prospective studies/
19. 15 or 16 or 17 or 18
20. 14 and 19

Search limited to human studies and English-language publications only. Filters excluded commentaries, letters, editorials and case reports.

Search Strategy for EMBASE

1. 'coronary artery disease'/de
2. 'coronary artery atherosclerosis'/de
3. 'coronary artery calcification'/
4. 'coronary artery constriction'/de
5. 'coronary artery spasm'/de
6. 'coronary artery obstruction'/de
7. 'coronary artery thrombosis'/de
8. 'no reflow phenomenon'/de AND
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. 'positron emission tomography'/de
11. 'single photon emission computer tomography'/de
12. 'gated single photon emission computed tomography'/de
13. 'radiopharmaceutical agent'/de
14. 10 or 11 or 12 or 13
15. 9 and 14

Search limits included:

- publication year (1996 – 2013)
- humans
- English language
- publication type (exclusions included editorial, letter, short survey, note and erratum)

APPENDIX C

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Asymptomatic, High Risk									
Young LH (2009) Design: Randomized Trial (Multiple tested groups) Setting: Multicenter outpatient (DIAD study)	Group with screening + 5 yr follow-up Group without screening+5 yr follow-up Mean (SD) follow-up=4.8 (0.9) years	Total n= 1,123 No Screening Mean (SD) age:60.8(6.4) Males:55% Non white:23% Diabetes duration (SD),yrs:8.9(6.9) BMI (SD):31(6.1) Family history of premature CAD:17% Screening Mean (SD) age:60.7(6.7) Males:52% Non white:22% Diabetes duration (SD),yrs:8.2(7.1) BMI (SD):31.1(6.5) Family history of premature CAD:21%	Risk: NR Asymptomatic diabetic patients: 100% No known or suspected CAD	Inclusion •Type 2 diabetes with age onset≥30 yrs and no ketoacidosis •Age 50-75 yrs Exclusion •Angina or equivalent symptoms •Stress test or ICA within 3 yrs of study •MI, revascularization or HF •Evidence of MI or LBBB •Bronchospasm	SPECT •Same day protocol if BMI<30 kg/m2 else two day protocol •Bruce protocol •Adenosine •Gating: yes •AC: NR	Revascularization <120 days No screening: 0.36% Screening: 1.6% p-value:0.03 Primary events, MI, cardiac death, secondary events, PTCA, CABG, All-cause death, stroke, HF, UA, revascularization in No screening group vs. screening group=NS	NR	Good Blinded committee adjudicated cardiac events Intent to treat analysis done Loss on follow up:3% at 3.5 yrs	Not to be screened group Incomplete follow-up:7.6% Screened group Refused:3.9% Not screened:6.9% Unable to schedule screening within 3 mo:2.8% Poor quality results:0.1% Incomplete follow-up:6.7%

SD: Standard deviation;BMI: Body mass index;CAD: Coronary artery disease; NR: Not reported; ICA: Invasive coronary angiography; MI: Myocardial infarction; HF: Heart failure; LBBB: Left bundle branch block; AC: Attenuation correction; HR: Hazard ratio; UA: Unstable angina; PTCA: Percutaneous transluminal coronary angiography; CABG: Coronary artery bypass grafting; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Symptomatic, Low-Intermediate Risk									
Shaw LJ (2011) Design: Randomized trial (Multiple tested groups) Setting: 43 cardiology practices (WOMEN Trial)	ETT SPECT w/multiple procedures • Tc-99m tetrofosmin • Thallium • No pharmacologic stressor used Follow-up: 24 months	Total n = 772 ETT: n:388 Median age: 63 (60,69) Female: 100% BMI: 27.4 (24.2, 30.9) Family history: 47.3% HTN: 55.2% Diabetes: 12.6% Stress SPECT: n=384 Median age: 62 (58,68) Female: 100% BMI: 27.4 (24.6, 31.8) Family history: 45.8% HTN: 52.0% Diabetes: 14.2%	Pre-test likelihood by ACC/AHA guidelines Intermediate risk: 100% Symptomatic :100% Suspected CAD: 100%	Inclusion: • Typical/atypical chest pain or ischemic equivalents (e.g. dyspnea) • Interpretable baseline ECG • Age ≥40 years or postmenopausal • Capable of performing ≥5 metabolic equivalents on the DASI questionnaire • Intermediate pre-test likelihood of CAD Exclusion: • Known CAD (history of MI or catheterization w/a >50% lesion in ≥1 coronary artery • ≤5 metabolic equivalents on the DASI • Pregnant/nursing women • Nuclear medicine study w/in 10 days of study • Electrocardiographic abnormalities such as LBBB, ventricular pacemaker • Significant valvular disease (e.g. severe aortic stenosis) • Uncontrolled HTN (>210/110 mmHg) • Hypotension (<90/60 mmHg) • History of heart failure • LVEF <50% • Patients receiving digoxin therapy	ETT: • Standard or modified Bruce protocol • Blood pressure, 12-lead ECG monitoring SPECT: • 3 potential protocols w/Tc-99m: 1) Rest-thallium/stress-tetrofosmin 2) 2-day tetrofosmin 3) 1-day tetrofosmin (rest/stress sequence) • Gating: when possible • AC: advised, but optional • Visual scoring w/aid of quantitative programs	Primary outcome: MACE at 2 years Results: MACE-free survival • ETT : 98% • SPECT : 98% • p:0.59 Secondary outcomes: Hospitalizations for CP, all-cause death Results: Hospitalizations • ETT : 3% • SPECT : 4% • p:0.39 All-cause death • ETT : 0.5% • SPECT : 1% • p:0.39	Exertional symptoms Chest pain ETT:13% SPECT:12% (p=NS) Dyspnea ETT:37 SPECT:42 (p=NS) Fatigue ETT:51 SPECT:53 (p=NS)	Fair No Intent to treat analysis done ECG/SPECT interpretation conducted by site investigators	Evaluation of angina symptoms by SAQ Average ionizing radiation during SPECT: 14 mSv • Dual-isotope: 24 mSv • Rest/stress 10 mSv

ETT: Exercise treadmill test; SPECT: Single photon emission computed tomography; ECG: Electrocardiogram; SD: Standard deviation;HTN: Hypertension; BMI: Body mass index; CAD: Coronary artery disease; DASI: Duke activity status index; LVEF: Left ventricular ejection fraction; AC: Attenuation correction; MACE: Major adverse cardiovascular event; CP: Chest pain; SAQ: Seattle angina questionnaire; N: Number; ACC; American College of Cardiology; AHA: American Heart Association; LBBB: Left bundle branch block

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Mishra JP (1998) Design: Retrospective Cohort (Multiple tested groups) Setting: NR	Group 1 : ICA as initial screening test Group 2 : SPECT as initial screening test	Group 1 (ICA as screening test) n= 4,572 Mean (SD)age:59(11) Males:62% HTN:44% Diabetes:14% Single-vessel Disease:28% Multi-vessel disease:72% Group 2 (SPECT as screening test) n=2,022 Mean (SD) age:57(12) (p>0.001) Males:55% (p>0.005) HTN:42% (p=NS) Diabetes:10% (p=NS) Single-vessel Disease:28% Multi-vessel disease:71%	Pryor et al method of risk assessment Intermediate risk:100% Symptomatic: 100% Suspected CAD: 100%	Inclusion •Evaluated for chest pain symptoms due to CAD Exclusion •Previous revascularization. •Cardiomyopathy •Valvular heart disease	SPECT •Thallium-201 •Bruce protocol for stress test •Gating: NR •AC: no	CAD prevalence: Group 1: 67% Group 2: 92% (of 20% referred to ICA) revascularization in CAD patients Group 1: 51% Group 2: 38% (p<0.0001) revascularization in total group Group 1:35% Group 2:6% (p<0.001)	NR	Poor No masking mentioned; Retrospective study; pre-test likelihood higher in group 1 and prevalence of multivessel disease higher in Group 2, no adjustment for confounding done	
Chang MS (2010) Design: Retrospective cohort (Multiple tested groups) Setting: Inpatient and outpatient	Stress only protocol Stress and rest protocol Follow-up: 4.76 yrs (mean)	Total n= 16,854 Mean(SD) age :59.2(13) Male :44% Diabetes:27% HTN :64.3% Stress Only n= 8,034 Mean (SD) age:59.8(13) Male:37% Diabetes:25.6% HTN :62.5% Stress and rest n= 8,820 Mean(SD) age:58.7(13) (p<0.001) Male:50% (p<0.001) Diabetes:28.2% (p<0.001) HTN :65.9% (p<0.001) Hyperlipidemia, smoking, history of MI, history of CAD p<0.001 between groups	Based on Duke Treadmill Score Low-risk: 78% Intermediate Risk: 22% Symptomatic Chest pain:73% Exertional Dyspnea: 5.9% Known CAD:27%	Inclusion Patients with normal SPECT images	SPECT: •Same day or two day •Stress only or Rest/stress protocol •Exercise stress or adenosine or dobutamine •99m Tc-tetrofosmin or 99m Tc-sestamibi •Gating: yes •AC: yes	All cause mortality between groups and sub groups compared (p=NS between groups) See notes, radiopharmaceutical dose for stress vs. stress-rest protocol	NR	Fair Retrospective cohort, no masking mentioned; not all important outcomes considered	Radiopharmaceutical dose Tc-99m tracer dose(mCi) •Total:39±20 •Stress-only:21.3±10.7 •Stress and rest:55.1±11.9 (p<0.001) Low dose Tc-99m Stress-only imaging (mCi) •Total:13.5±2 •Stress-only:13.5±2 •Stress and rest:55.1±11.9 (p<0.001)

SPECT: Single photon emission computed tomography; ICA: Invasive coronary angiography;SD: Standard deviation;HTN: Hypertension; CAD: Coronary artery disease; AC: Attenuation Correction; NS: Not significant; NR: Not reported; N: Number; MI: Myocardial infarction

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Olmos LO (1998) Design: Retrospective cohort (same cohort, multiple tests) Setting: NR	SPECT •Thallium-201 Stress Echo Follow-up: 3.7±2 yrs (mean)	N=248 Mean(SD)age: 56.3(12) Male:76% Diabetes:17% HTN:39% Obesity:17%	Low Risk: 58% Intermediate risk: 18% High risk: 24% (Risk assessment method NR) Symptomatic: 31% Known CAD: 23%	Exclusion •Recent MI •Cardiac transplant •Cardiomyopathy or valvular disease	ETT •Bruce protocol Exercise Echo •2-D Echo at rest and after stress •16 segment model •Wall motion score index obtained SPECT •Rotating gamma camera(ADAC, ARC 3000-3300) •Gating and AC: NR	Predictors of ischemic events and cardiac death •Clinical parameters+ECG+SPECT model Variable: Abnormal scan OR:2.76 p-value:0.03 95% CI:1.08-7.07 •Clinical parameters+ECG+Echo model Variable: Abnormal scan OR:2.69 p-value:0.04 95% CI:1.04-6.96 Predictors of cardiac death	NR	N/A	
						•Clinical parameters+ECG+SPECT model Variable: Perfusion defect size (per 10 unit increment) OR:1.41 p-value:0.007 95% CI:1.1-1.82 •Clinical parameters+ECG+Echo model Variable: Wall motion score index (per unit increment) OR:3.95 p-value:0.03 95% CI:1.12-13.89 Rate(% per year exposure for 5.5yrs) Hospitalization for UA: Echo:0.24			
						SPECT:0.32 Revascularization Echo:0.4 SPECT:0.32 All cardiac events Echo:1.05 SPECT:1.13			

SPECT: Single photon emission computed tomography; ECHO: Echocardiography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; MI: Myocardial infarction; ETT: Exercise treadmill test; ECG: Electrocardiogram; AC: Attenuation correction; NR: Not reported; CI: Confidence interval; OR: Odds ratio; UA: Unstable angina; N: Number; N/A: Not applicable

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Symptomatic, High Risk									
Sabharwal NK (2007) Design: Randomized trial (Multiple tested groups) Setting: Outpatients, Hospital chest pain clinic	ETT: Stress SPECT: • Tc-99m sestamibi •Exercise, dipyridamole, or dobutamine stress Follow-up: 24 months	Total n = 457 ETT: n=207 Mean (SD) age: 58.9 (11.4) Male: 57.5% Family history: 46.3% HTN: 46.3% Mean (SD) BMI: 27.6 (4.6) Diabetes: 14.5% Exercise SPECT: n=250 Mean (SD) age: 59.7 (12.2) Male: 55.6% Family history: 43.3% HTN: 53.2% Mean (SD) BMI: 26.9 (4.5) Diabetes: 19.2%	Pre-test likelihood by ACC/AHA guidelines Pretest likelihood: • Low: 11% • Intermediate: 71% • High: 18% Symptomatic: 100% Suspected CAD: 100%	Inclusion: • Age >25 • Suspected CAD Exclusion: • Acute coronary syndromes • Known CAD • Pregnant or lactating • Abnormal resting EKG	ETT: • Symptom-limited or modified Bruce protocol • Blood pressure, 12-lead EKG monitoring Exercise MPI: • Tc-99m sestamibi •Exercise, dipyridamole, or dobutamine stress •Stress/rest protocol (if stress test abnormal) •Dual head gamma camera (Sopha DS7) • Gating: Yes • AC: NR • Semiquantitative visual interpretation	Referral to revascularization ETT:38% SPECT:66% (p<0.005)	NR	Fair No masking; all patients did not undergo ICA	Equivocal Treadmill test ETT:39% SPECT:14% 1 cardiac death in ETT arm

ETT: Exercise treadmill test; SPECT: Single photon emission computed tomography; EKG: Electrocardiogram; SD: Standard deviation; BMI: Body mass index; CAD: Coronary artery disease; AC: Attenuation correction; ICA: Invasive coronary angiography; N: Number; HTN: Hypertension; ACC; American College of Cardiology; AHA: American Heart Association; NR: Not reported

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Hachamovitch R (2012) Design: Prospective registry design (Multiple tested groups) Setting: 41 different centers (SPARC study)	SPECT PET CCTA Follow-up:90 days	Total n= 1,703 Mean (SD)age:62(11) Male:48% Caucasian:82% BMI(SD)(kg/m^2):31(7) Diabetes:29% HTN:64% SPECT n=565 Mean(SD) age:60(11) Male:49% White:68% BMI(SD)(kg/m^2):30(7) Diabetes:31% HTN:66% Family History:29% PET n=548	Pre-test likelihood by ACC/AHA guidelines Intermediate to high likelihood=100% Symptomatic :89% Suspected CAD: 100%	Inclusion •Clinically referred stress SPECT, stress PET, CTA and PET-CT •Intermediate to high pre-test likelihood of CAD based on ACC/AHA stable angina guidelines Exclusion •Low pre-test likelihood of CAD •Major concomitant non-cardiac disease •Cardiac myopathy •Chest pain at rest within 48 hours of index test	Each study center followed own protocol for imaging	Frequency of CAD after ICA SPECT: 54.2% PET:67.2% CCTA:61.5% (P=0.51) Positive index test, no CAD on ICA SPECT: 39.1% PET:28.3% CCTA:16.9% (SPECT vs. PET, p=NS, SPECT vs. CCTA, p=0.049) Negative test, index test, CAD on ICA SPECT: 0% PET:3.3% CCTA:20.8% (SPECT vs. PET, p=NS, SPECT vs. CCTA, p=0.006)	NR	Good Open-label multi-center study;CAD results interpreted by 2 independent readers	Lost to follow-up:0.3% Withdrew consent: 0.5%
		Mean (SD)age:63(11) (p<0.05 vs. SPECT) Male:41% (p<0.05 vs. SPECT) White:80% (p<0.05 vs. SPECT) BMI(SD)(kg/m^2):34(10) (p<0.05 vs. SPECT) Diabetes:41% (p<0.05 vs. SPECT) HTN:73% (p<0.05 vs. SPECT) Family History:24% (p<0.05 vs. SPECT) CCTA n=590 Mean (SD)age:58(11.4) Male:52% White:87% BMI (SD)(kg/m^2):29(6)				Multivariable Modeling results •Variable:CCTA vs. SPECT p-value:<0.0001 Odds Ratio(95% CI) :14.92(3.52-63.27) •Variable:PET vs. SPECT p-value:0.045 Odds Ratio:5.03(1.04-24.43)			
		Diabetes:16% HTN:56% Family History:37% (p<0.05 vs. SPECT)							

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; CCTA: Coronary computed tomography angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; CT: Computed tomography; CAD: Coronary artery disease; ICA: Invasive coronary angiography; NS: Not significant; ACC; American College of Cardiology; AHA: American Heart Association; NR: Not reported; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Borges-Neto S (2004) Design: Retrospective Cohort (Multiple tested groups) Setting: University Medical Center, Inpatient/ Outpatient: NR	^{99m} Tc-Tetrofosmin ^{99m}Tc-Sestamibi Follow up: 1.5 yrs (Median)	n = 1,818 <u>99m Tc-Tetrofosmin Group</u>: n = 903 Median age : 63 Male :65% Diabetes : 33% HTN : 67% Exercise stress :52% <u>99mTc-Sestamibi Group</u>: n = 915 Median age : 63 Male : 66% (p=NS) Diabetes : 29% (p=NS) HTN:67% (p=NS) Exercise stress :57% (p=NS)	High risk:100% (Risk assessment method NR) Symptomatic: 100% Known vs. Suspected CAD: NR	<u>Inclusion criteria:</u> • ICA 180 days before or after nuclear test	<u>SPECT:</u> •Same day rest/stress protocol •AC: no •Gating: no <u>ETT:</u> •Bruce Protocol • Cardiac medications avoided 48 hours prior to exercise test	<u>Cardiovascular death</u> •Total cardiovascular deaths : 68 (62% of total deaths) •Tetrofosmin : 4.4% •Sestamibi : 4.6% (p =NS) <u>Mortality rate:</u> •Overall mortality rate : 7.1% •Tetrofosmin : 6.5% •Sestamibi : 7.5% (p =NS)	NR	Fair No blinding during image interpretation	
Schinkel AFL (2004) Design: Cohort (same cohort, multiple tests) Setting: Thoraxcenter, Inpatient/ outpatient: NR	<u>SPECT</u> •99m Tc-Sestamibi •Dobutamine <u>Stress Echo</u> Follow-up: 7.3±2.8 yrs (mean)	n= 301 Mean age: NR Male:56% Diabetes:14% HTN:44%	Diamond-Forrester Method Low pre-test probability: 2% Intermediate pre-test probability: 72% High pre-test probability: 26% Known or suspected CAD: 100%	<u>Inclusion</u> •Unable to perform ETT	<u>SPECT</u> •Gammasonics single-head camera (Siemens) •Gating: NR •AC: no <u>Echo</u> •2-D echo at stress, rest and recovery	<u>Multivariate Predictors from Cox model:</u> <u>•Cardiac death</u> Abnormal Nuclear Scan HR: 4.4 95% CI:1.2-12 Abnormal Echo HR:3.4 95% CI:1.2-12 <u>•Cardiac events</u> Abnormal Nuclear Scan HR: 3.1 95% CI:1.1-8.9 Abnormal Echo HR: 2.6 95% CI:1.1-6.2	Non sustained ventricular tachycardia: 4% Atrial fibrillation: 1% Headache: 5% Nausea: 5% Hypotension: 0.7% Incomplete test due to side effects: 6%	N/A	

HTN: Hypertension; NS: Not significant; NR: Not reported; CAD: Coronary artery disease; ICA: Invasive coronary angiography; SPECT:Single photon emission computed tomography; ETT: Exercise treadmill test; ECHO: Echocardiogram; CI: Confidence interval; HR: Hazard ratio; N: Number; N/A: Not applicable

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Pazhenkottil AP (July:2011) Design: Cohort (Same cohort, multiple tests) (Patient overlap with Pazhenkottil AP-Feb 2011) Setting: NR	Agreement of image results from SPECT CCTA Fused SPECT/CCTA results used by physician to make decisions regarding ICA or conservative treatment Matched results=reversible defect on SPECT, showing ≥50% narrowing of coronary luminal diameter on CCTA Unmatched: Unmatched finding from SPECT and/ or CCTA	n=318 Mean age:61±11 Males:67% Diabetes:14% HTN: 56% Family history: 27%	Diamond Forrester Method Low Risk: 10% Intermediate risk:73% High risk: 17% Symptomatic: 18% Known CAD:21%	NR	<u>SPECT</u> •Single day protocol •99M-Tc Tetrofosmin •Adenosine stress •Dual head gamma camera (Millenium VG and Hawkeye or Ventri) •Gating: NR •AC: yes <u>CCTA</u> •64-Slice CT scanner (LightSpeed VCT) •iv metoprolol to stabilize HR SPECT and CCTA 1±3 days apart Images fused on Advantage Workstation 4.3	Ref to revascularization after ICA (matched group) PCI=64.5% CABG=3% revascularization rate:41% Ref to revascularization after ICA (unmatched group) PCI=40% CABG=13.3% revascularization rate:11% (p<0.001 vs. 'matched' images) Ref to revascularization after ICA PCI=40% CABG=13.3% revascularization rate:11% (p<0.001 vs. 'matched' images) Yield of CAD per angiography matched:90% unmatched:68% PCI rate per angiography matched:80% unmatched:53%	NR	N/A	Effective radiation dose for SPECT:10.1±0.1 mSv Estimated radiation dose for CCTA:17.9±5.8 mSv Prospectively triggered CCTA effective radiation dose:1.9±0.5 mSv (n=70) Effective radiation dose for SPECT/CT:12 mSv

SPECT: Single photon emission computed tomography; CCTA: Coronary computed tomography angiography; ICA: Invasive coronary angiography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; NR: Not reported; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; N: number; N/A: Not applicable; AC: Attenuation correction: CT: Computed tomography

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Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Pazhenkottil AP (Feb:2011) Design: Cohort (Same cohort, multiple tests) Setting: NR	Agreement of image results from SPECT CCTA Fused SPECT/CCTA results used by physician to make decisions regarding ICA or conservative treatment Matched results=reversible defect on SPECT and CCTA showing ≥50% narrowing of coronary luminal diameter	n=302 Mean (SD) age:61(11) Males:67% Diabetes:14% HTN: 57% Family history: 27% Obesity: 20%	Diamond Forrester Method Low Risk: 9% Intermediate risk:76% High risk: 15% Symptomatic: 18% Known CAD:21%	Exclusion: revascularization within 30 days of enrollment	<u>SPECT</u> •Single day protocol •99M-Tc Tetrofosmin •Adenosine stress •Dual head gamma camera (Millenium VG and Hawkeye or Ventri) •Gating:yes •AC: yes <u>CCTA</u> •64-Slice CT scanner (LightSpeed VCT) •iv metoprolol to stabilize HR SPECT and CCTA 2±10 days apart	First year rates of death or MI Matched:8.1% Unmatched: 5.8% First year rates of MACE Matched:27% Unmatched:11.7% Annual rate of MACE Matched:21% Unmatched:7% (P<0.001) <u>Multivariate Analysis</u> ≥50% Stenosis HR:3.12 (p<0.001)	NR	N/A	Effective radiation dose for SPECT:10.3±1.8 mSv Estimated radiation dose for CCTA:15.9±4.9 mSv Prospectively triggered CCTA effective radiation dose:1.8±0.6 mSv (n=70)
	Unmatched: Unmatched finding from SPECT and/ or CCTA Follow-up:2.8 yrs				Images fused on Advantage Workstation 4.3	Matched finding HR:3.8 (p=0.002)			

SPECT: Single photon emission computed tomography; CCTA: Coronary computed tomography angiography; ICA: Invasive coronary angiography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; MACE: Major adverse cardiovascular events; HR: Hazard ratio; N: number; N/A: Not applicable; AC: Attenuation correction

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Known CAD									
Bourque JM(2004) Design: Retrospective Cohort (Multiple tested groups) Setting: University Medical Center, Inpatient/Outpatient NR	No nuclear study Nuclear study before ICA Nuclear study after ICA Follow-up: NR	<u>No nuclear study</u> n= 2,335 Median age:65 Male:72.6% White:77.8% Diabetes:36.8% HTN:64.2% <u>Nuclear study before ICA</u> n= 239 Median age: 64 Male:76.2% White:71.5% Diabetes:42.3% HTN:76.2% <u>Nuclear study after ICA</u> n= 377 Median age:64 (p=NS between groups) Male:70.8% (p=NS between groups) White:76.9% (p<0.012) Diabetes:35.8% (p=NS between groups) HTN:60.5% (p<0.001)	High risk Symptomatic: NR Known CAD: 100%	<u>Inclusion:</u> •LVEF≤40% •Stenosis ≥75% in at least 1 major epicardial vessel <u>Exclusion</u> •Transient HF, acute MI, PCI or CABG between ICA and SPECT •Valvular heart disease •Congenital heart disease	<u>SPECT</u> •Same day stress/rest or rest/stress protocol •99m Tc-sestamibi Dobutamine, dipyridamole or adenosine •Gating: yes •AC: no <u>ICA</u> •Multiple left and right anterior oblique projections and biplane LVG •Stenosis graded on ordinal scale of 0%, 25%, 50%, 75%, 95% and 100% •LVEF determined by ventriculography	Subsequent rate of revascularization. All revascularization No nuclear study:53.2% Nuclear study before ICA:45.6% Nuclear study after ICA:35.8% (p<0.001) CABG No nuclear study:30.3% Nuclear study before ICA:21.3% Nuclear study after ICA:20.2% (p<0.001) PCI No nuclear study:27% Nuclear study before ICA:27.6% Nuclear study after ICA:18% (p<0.001) Days to subsequent revascularization (median) All revascularization No nuclear study:2 Nuclear study before ICA:2 Nuclear study after ICA:14 (p<0.001) Days to subsequent CABG (median) No nuclear study:4 Nuclear study before ICA:5 Nuclear study after ICA:13 (p<0.001) Days to subsequent PCI (median) No nuclear study:0 Nuclear study before ICA:1 Nuclear study after ICA:102 (p<0.001)	NR	Fair Retrospective cohort, no masking mentioned Selection bias, only those with known CAD included	

ICA: Invasive coronary angiography; NR: Not reported; HTN: Hypertension; NS: Not significant; CAD: Coronary artery disease;HF: Heart failure; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AC: Attenuation correction; LVG: Left ventriculography; LVEF: Left ventricular ejection fraction; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Adams G.L. (2007) Design: Prospective Cohort (multiple tested groups) Setting: NR	^{99m} Tc-Tetrofosmin ^{99m}Tc-Sestamibi • Adenosine or Dipyridamole Follow-up: 4 yrs(Median)	Total n = 2147 99m Tc-Tetrofosmin Group: n =1128 Median age : 67 Male : 57.3% Diabetes : 40.3% HTN : 75.3% 99mTc-Sestamibi Group: n = 1019 Median age : 67 Male : 52.4% (p=0.02) Diabetes : 40.4%(p=NS) HTN : 74.4%(p=NS)	High risk Symptomatic: NR Known CAD:100%	Inclusion: •Catheterization before or after SPECT	SPECT: •Rest/stress same day protocol •Two camera systems used - Three headed gamma camera(Triad XLT™) -Two-headed gamma camera(Cardinal™) •Gating:NR •AC: no	Unadjusted Overall mortality rate:p=0.62 Cardiovascular death rate: p=0.96 p values for Interaction between SSS and agent -For death:0.3667 -For cardiovascular death:0.1236	NR	Fair MI not considered as outcome Selection bias as only those with known CAD included	

HTN: Hypertension; CAD: Coronary artery disease; SPECT: Single photon emission computed tomography; NR: Not reported; SSS: Summed stress score; MI: Myocardial infarction; NS: Not significant; N: Number; AC: Attenuation correction

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Mixed Risk									
Sharples L (2007) Design: Randomized Trial (Multiple tested groups) Setting: Tertiary cardiothoracic referral center	SPECT MRI stress-ECHO ICA (controls) Follow up:18 months	<u>SPECT</u> n=224 Mean(SD) age:62.1(9.5) Males:70% Mean (SD)BMI:27.3(4.3) Family history of CAD:8% Treated HTN: 59% <u>MRI</u> n=226 Mean(SD) age:62.2(9) Males:68% Mean(SD) BMI:28(4.4) Family history of CAD:9% Treated HTN: 51% <u>stress-ECHO</u> n=226 Mean(SD) age:61.9(9.9) Males:71% Mean(SD) BMI:27.9(4.2) Family history of CAD:10% Treated HTN: 57% <u>ICA</u> n=222 Mean (SD)age:60.7(9.1) Males:67% Mean BMI:27.6±4.2 Family history of CAD:27% Treated HTN:53%	Pryor Risk assessment High: 69% in all groups Symptomatic:% NR Known CAD: NR	<u>Inclusion:</u> •Known or suspected CAD, referred for ICA and ETT results indicate referral to ICA <u>Exclusion:</u> •MI<3 months •Functional test <12 months •UA or urgent revascularization •Physically unable to perform ETT •Not available by telephone	SPECT •Two day rest-stress protocol •Adenosine •Gating: When available •AC: NR MRI •1.5-t MAGNET SYSTEM (Signa CV/I, GE Medical Systems) •Stress-rest protocol •Adenosine stress-ECHO •Standard protocol increasing dobutamine dose at 3 minutes duration •Intravenous ultrasound contrast(microspheres) ICA •50% stenosis in left main stem or 70% stenosis in any other major vessel=significant CAD •Seldingers technique; femoral route	<u>CABG</u> SPECT and stress-ECHO:13% MRI: 11% ICA:10% <u>PCI</u> SPECT: 18% MRI and stress-ECHO: 23% ICA: 25% <u>Cardiac death</u> SPECT:0.02 % MRI:0,01% stress-ECHO:0.004 % ICA: 0.01% <u>Other Cardiovascular death</u> SPECT:0 % MRI:0.01% stress-ECHO:0.008 % ICA: 0% <u>Total non-fatal events</u> (includes admission for chest pain, acute MI, unplanned PCI, unplanned CABG and others** SPECT:24% MRI:29% Stress-ECHO:31% ICA:19%Relative Rate of non fatal events in stress-ECHO vs. ICA=1.05; p=0.012 **others: post CABG wound infection, breathlessness, admission for fluid over the heart, transient ischemic attack	SPECT: No adverse events during test MRI: Arrhythmia: 2 (0.008%)patients Echo: Administration error:1 (0.004%)patient Failed test (due to inadequate achievement of stress, HTN, obesity or arrhythmia): 8(0.035%) patients	Fair Patients, clinicians, technicians and research assistants not blinded to group allocation	Equivocal results SPECT:6% (p=0.05 vs. ICA) MRI:22%% (p<0.001 vs. ICA) stress-ECHO:10% (p<0.001 vs. ICA) ICA:2%

SPECT: Single photon emission computed tomography; MRI: Magnetic resonance imaging; ECHO: Echocardiography; ICA: Invasive coronary angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; NR: Not reported; CAD: Coronary artery disease; ETT: Exercise treadmill test; MI: Myocardial infarction; UA: Unstable angina; AC: Attenuation correction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Mullani NA (2000) Design: Randomized trial Setting: Imaging center (multiple tested groups)	SPECT •Dual isotope,99m Tc-Sestamibi and Thallium-201 •Dipyridamole PET •Rubidium-82 •Dipyridamole Follow-up:9 months (mean)	Total=210 Men:49.5% Women:50.5% Men Mean (SD)age: 62(11) HTN:45% Family history of CAD:18% Women Mean(SD) age: 66(12) (p=0.004) HTN:52% Family history of CAD:19.8%	Risk: NR Symptomatic: 100% Known CAD PET:30% SPECT:30%	Inclusion •For patients with CAD: CAD documented by ICA and symptoms For patients without CAD: Symptoms of CAD	SPECT •Rest/stress protocol •Gating and AC: NR PET •Gating: NR •AC: yes	Multiple Logistic Regression Analysis of Positive Scans Age OR:0.99 p-value:0.85 Sex (Male vs. Female) OR:4.04 p-value:0.001 Prior CAD vs. No OR:5.22 p-value:0.002 Modality (PET vs. SPECT) OR:1.29 p-value:0.42 Multiple Logistic	NR	Poor No masking of image interpretation	
						Regression Analysis of Positive Scans for patients with no prior CAD Age OR:1.00 p-value:0.70 Sex (Male vs., Female) OR:3.91 p-value:0.002 Modality:(PET vs. SPECT) OR:2.45;p-value:0.03			
						Multiple Logistic Regression Analysis of Positive Scans for patients with prior CAD Age OR:0.97 p-value:0.40 Sex (Male vs. Female) OR:2.29 p-value:0.15 Modality (PET vs. SPECT) OR:0.45 p-value:0.15 Cardiac death at 9 mo. SPECT:3% PET: 4% (p=NS)			

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; SD: Standard deviation; CAD: Coronary artery disease; ICA: Invasive coronary angiography; AC: Attenuation correction; NR: Not reported OR: Odds ratio; N: Number; HTN: Hypertension; NS: Not significant

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Merhige M (2007) Design: Prospective Cohort (Multiple tested groups) Setting: Outpatient	SPECT •99.Tc-Sestamibi PET •Rubidium-82 Follow-up:1year	SPECT n=102 Median (SD)age:62(11) Male:54% PET n=2,159 Median (SD)age:66(8) Male:54%	Risk: NR Symptomatic: NR Known CAD: SPECT: 44% PET: 49%	Inclusion: •Patients with moderate pre-test likelihood of CAD in PET arm Exclusion: •Patients with pretest likelihood <0.11 or >0.70 (CADENZA computer program)	SPECT •One-day or two-day protocol •Dual-headed gamma camera(CardiaL;ElScint) •Gating: Yes •AC: NR PET •HZL/R camera •Gating: NR •AC: Yes	PTCI rate SPECT:0.029 PET:0.028 (p=NS) Cardiac Mortality rate SPECT:0.02 PET:0.008 (p=NS)+H78 Acute MI rate SPECT:0.029 PET:0.011 (p=NS) Revascularization rate SPECT:0.114 PET:0.06 (p<0.01) CABG rate SPECT:0.07 PET:0.03 (p<0.01)	NR	Good Image interpretation done independent of clinical data	

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; SD: Standard deviation; NR: Not reported; CAD: Coronary artery disease; AC: Attenuation correction; PTCI: Percutaneous transluminal coronary intervention; MI: Myocardial infarction; CABG: Coronary artery bypass grafting; NS: Not significant; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Basic D (2006) Design: Prospective Cohort (same cohort, multiple tests) Setting: Hospital, Inpatient/ Outpatient: NR	ECHO •Optison •Definity SPECT •99M Tc Sestamibi •Dipyridamole Follow-up: 29 months (range 6-39 months)	n= 51 Mean (SD)age:60(11) Male:67% Diabetes:17.6% HTN:56.8% Family history CAD:15.6% History of CHF, smoking and prior revascularization significantly different btw groups.	Risk: NR Symptomatic Chest pain: 100% Known or suspected CAD	Inclusion: •Known or suspected CAD Exclusion •Valvular disease or cardiomyopathy	SPECT •Same day stress/rest protocol •Gating:NR •AC: yes ECHO •HDI 5000cv scanner and P4-2 scan head or Sonos 550 scanner with S-3 scan head used	Cardiac Event Rate (Among patients with abnormal results) •SPECT:25% •ECHO: 29% Cumulative event free survival(among patients with abnormal results) •SPECT:73.9%(log rank p<0.05) •ECHO: 70.8% (log rank p<0.005)	NR	N/A	
De Lima JJ (2003) Design: Prospective Cohort (Multiple groups) Setting: NR	SPECT •Tc-99m Methoxyisobutylisonitrile •Dipyridamole Stress ECHO •Dobutamine Risk stratification •High risk(at least one significant cardiovascular condition, history of MACE or diabetes) •No high risk ICA •≥70% stenosis in one or more epicardial arteries by visual analysis analysis Mean follow-up: 26 months	n=126 Mean (SD)age: 55.1(7.8) Males: 77% Whites:67% Diabetes:30% HTN:95%	% symptomatic or asymptomatic: NR Renal Transplant candidates=100% Significant CAD (≥70% stenosis)=42% Intermediate-high risk	Inclusion At least one of the following: •age≥50 yrs •Diabetes •Angina •Previous MI or stroke •LV dysfunction •Extra cardiac atherosclerosis	SPECT: Test protocol NR Stress-ECHO: •HDI 5000 apparatus used	Cardiac Events •SPECT Transient or fixed defects Positive:18.2% Negative:9% (p=NS) •Stress echo Positive:16.7% Negative:13% (p=NS) •Risk stratification High risk:21.3% No high risk:6.2% (p=0.008) •ICA Positive:27.3% Negative:3.2% (p=0.0004) Total Cardiac death: 14.3%	NR	N/A	Lost to follow-up = 3% Refused to continue protocol= 13% Non-cardiac death=19.8%

SPECT: Single photon emission computed tomography; ECHO: Echocardiography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; CHF: Congestive Heart failure; NR: Not reported; AC: Attenuation correction; N/A: Not applicable; MACE: Major adverse cardiac events; MI: Myocardial infarction, LV: Left ventricular; NS: Not significant; N: Number; ICA; Invasive coronary angiography

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Fietcher M (2012) Design: Prospective Cohort (same cohort, multiple tests) Setting: NR	SPECT/CCTA •Tc-99m Tetrofosmin •Dobutamine or adenosine ICA •Stenosis>50% = CAD Matched image: reversible defect on SPECT and stenosis≥50% No match: Normal images or unmatched findings between SPECT and/ or CCTA	n= 62 Mean (SD)age:62(10) Male:76% Mean (SD)BMI: 28(5) Diabetes:16% HTN:68% Family history CAD:35%	Risk: NR Known or suspected CAD Asymptomatic: 50%	Inclusion: •Patients referred for assessment of known or suspected CAD using same day SPECT and CCTA Exclusion •Prior CABG	SPECT/CCTA Hybrid •Same day protocol •Single session hybrid scan •CZT/64 slice hybrid camera •Gating: NR •AC: yes •Images fused on Advantage Workstation	Matched results (Defect in SPECT+CCTA):23 (38%) Unmatched(Defect in SPECT or CCTA):39(63%) revascularization post ICA Matched:91% Unmatched:8% (p<0.001)	NR	N/A	Effective radiation dose for stress/ rest SPECT:10.2±1.5 mSv Prospectively triggered CCTA effective radiation dose:1.8±0.6 mSv
Pattillo RW (1996) Design: Cohort (same cohort, multiple tests) Setting: NR	Treadmill exercise score Gensini score from ICA SPECT score Follow-up: 41±22 months	n= 732 Male:71% Mean (SD)age:59(11) years	Risk: NR Symptomatic: NR Known and suspected CAD: 100%	Exclusion •Previous CABG or PCI •MI within 3 months •Unstable angina •revascularization. Within 3 months	ETT •Bruce protocol •Angina score and ETT score obtained SPECT •201-Tl ICA stenosis≥50% stenosis=CAD	AUC SPECT:0.67 Gensini: 0.61 Treadmill exercise score:0.46 (p<0.05)	NR	N/A	

SPECT: Single photon emission computed tomography; CCTA: Coronary computed tomography angiography; ICA: Invasive coronary angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; NR: Not reported; CABG: Coronary artery bypass grafting; AC: Attenuation correction; N/A: Not applicable; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; AUC: Area under curve; N: Number

Table C1. Impact of cardiac nuclear testing on mortality and major cardiovascular events, by population.

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Harms	Quality	Notes
Hoque A (2002) Design: Prospective Cohort (same cohort, multiple tests) Setting: Hospital, Inpatient/ Outpatient: NR	SPECT •Thallium-201 •Exercise stress ECHO Follow-up:106±34.7 months	Total n=206 Mean (SD)age:56.8(9.9) Diabetes: 24.3% HTN: 64.1% Family history of CAD: 18.9%	Risk: NR Symptomatic: 100% Known or suspected CAD	Exclusion •revascularization within 3 months of stress test	SPECT •Single-day protocol •Bruce protocol for exercise stress •Gamma camera(Starcam 400 AC) •Gating and AC: NR Echo •Two dimensional imaging •Phased array echo machine (77020, Hewlett Packard)	Multivariate Predictors from Cox model: •Cardiac death Mod-large ischemia by echo: -5 yr follow-up RR: 17.6 95% CI:1.9-165 p-value:0.01 -10 yr follow up RR: 4.3 95% CI:1.8-10.6 p-value:0.001 Mod-large fixed nuclear defect -5 yr follow-up RR: 8.8	NR	N/A	
						95% CI:0.9-82.4 p-value:0.056 -10 yr follow up RR: 3.9 95% CI:1.6-9.8 p-value:0.003 10 year follow-up Over-all mortality: 33% Cardiac death: 13.6% MI: 14.6% UA: 21.8% Sudden death: 5.3%			

SPECT: Single photon emission computed tomography; ECHO: Echocardiography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; NR: Not reported; AC: Attenuation correction; RR: Relative risk; CI: Confidence interval; MI: Myocardial infarction; UA: Unstable angina; N/A: Not applicable; N: Number

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Asymptomatic, High Risk										
Young LH (2009) Design: Randomized Trial (Multiple tested groups) Setting: Multicenter outpatient	Group with screening + 5 yr follow-up Group without screening+5 yr follow-up Mean (SD) follow-up=4.8 (0.9) years	Total n= 1,123 No Screening Mean (SD) age:60.8(6.4) Males:55% Non white:23% Diabetes duration (SD),yrs:8.9(6.9) BMI (SD):31(6.1) Family history of premature CAD:17% Screening Mean (SD) age:60.7(6.7) Males:52% Non white:22% Diabetes duration (SD),yrs:8.2(7.1) BMI (SD):31.1(6.5) Family history of premature CAD:21%	Risk: NR Asymptomatic diabetic patients: 100% No known or suspected CAD	Inclusion •Type 2 diabetes with age onset≥30 yrs and no ketoacidosis •Age 50-75 yrs Exclusion •Angina or equivalent symptoms •Stress test or ICA within 3 yrs of study •MI, revasc or HF •Evidence of MI or LBBB •Bronchospasm	SPECT •Same day protocol if BMI<30 kg/m2 else two day protocol •Bruce protocol •Adenosine •Gating: yes •AC: NR	N/A	Additional stress test No screening:30% Screening: 21% (<0.001) ICA<120 days No screening:0.5% Screening:4.4% (p<0.001) Difference in medication use between groups at baseline and post 5 years=NS	NR	Good Blinded committee adjudicated cardiac events Intent to treat analysis done Loss on follow up:3% at 3.5 yrs	Not to be screened group Incomplete follow-up:7.6% Screened group Refused:3.9% Not screened:6.9% Unable to schedule screening within 3 mo:2.8% Poor quality results:0.1% Incomplete follow-up:6.7%

SD: Standard deviation; BMI: Body mass index; CAD: Coronary artery disease; NR: Not reported; ICA: Invasive coronary angiography; MI: Myocardial infarction; HF: Heart failure; LBBB: Left bundle branch block; AC: Attenuation correction; N: Number; N/A: Not applicable; NS: Not significant

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Symptomatic, Low-Intermediate Risk										
Shaw LJ (2011) Design: Randomized trial Setting: 43 cardiology practices (multiple tested groups)	ETT SPECT Follow-up: 24 months	Total n = 772 ETT: n=388 Median age: 63 (60,69) Female: 100% BMI: 27.4 (24.2, 30.9) Family history: 47.3% HTN: 55.2% Diabetes: 12.6% SPECT: n=384 Median age: 62 (58,68) Female: 100% BMI: 27.4 (24.6, 31.8) Family history: 45.8% HTN: 52.0% Diabetes: 14.2	Pre-test likelihood by ACC/AHA guidelines Intermediate risk: 100% Symptomatic :100% Suspected CAD: 100%	Inclusion: • Typical/atypical chest pain or ischemic equivalents (e.g. dyspnea) • Interpretable baseline ECG • Age ≥40 years or postmenopausal • Capable of performing ≥5 metabolic equivalents on the DASI questionnaire • Intermediate pre-test likelihood of CAD Exclusion: • Known CAD (history of MI or catheterization w/a >50% lesion in ≥1 coronary artery • ≤5 metabolic equivalents on the DASI • Pregnant/nursing women • Nuclear medicine study w/in 10 days of study • Electrocardiographic abnormalities such as LBBB, ventricular pacemaker • Significant valvular disease (e.g. severe aortic stenosis) • Uncontrolled HTN (>210/110 mmHg) • Hypotension (<90/60 mmHg) • History of heart failure • LVEF <50% • Patients receiving digoxin therapy	ETT: • Standard or modified Bruce protocol • Blood pressure, 12-lead ECG monitoring SPECT: • Tc-99m tetrofosmin • Thallium • No pharmacologic stressor used • 3 potential protocols w/Tc-99m: 1) Rest-thallium/stress-tetrofosmin 2) 2-day tetrofosmin 3) 1-day tetrofosmin (rest/stress sequence) • Gating: when possible • AC: advised, but optional • Visual scoring w/aid of quantitative programs	N/A	Downstream procedural use • Follow-up exercise-ECG testing: ETT: 2 patients SPECT: 1 patient • Crossover to SPECT or repeat SPECT: ETT: 17.7% SPECT: 9.3% p<0.0001 • Referral to angiography: ETT: 6.4% SPECT: 7.3% no p-value reported • Follow-up coronary revascularization: ETT: 1.0% SPECT: 2.2% p=0.16 • No additional diagnostic testing: ETT: 81% SPECT: 89% p<0.0001	Exertional symptoms Chest pain ETT:13% SPECT:12% (p=NS) Dyspnea ETT:37 SPECT:42 (p=NS) Fatigue ETT:51 SPECT:53 (p=NS)	Fair No Intent to treat analysis done ECG/SPECT interpretation conducted by site investigators	

ETT: Exercise treadmill test; SPECT: Single photon emission computed tomography; ECG: Electrocardiogram; HTN: Hypertension; BMI: Body mass index; CAD: Coronary artery disease; DASI: Duke activity status index; LVEF: Left ventricular ejection fraction; AC: Attenuation correction; N/A: Not applicable; N: Number; NS: Not significant; ACC: American College of Cardiology; AHA: American Heart Association

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Mishra JP (1998) Design: Retrospective Cohort (Multiple tested groups) Setting: NR	Group 1 : ICA as initial screening test Group 2 : SPECT as initial screening test	Group 1 (ICA as screening test) n= 4,572 Mean (SD)age:59(11) Males:62% HTN:44% Diabetes:14% Single-vessel Disease:28% Multi-vessel disease:72% Group 2 (SPECT as screening test) n=2,022 Mean (SD) age:57(12) (p>0.001) Males:55% (p>0.005) HTN:42% (p=NS) Diabetes:10% (p=NS) Single-vessel Disease:28% Multi-vessel disease:71%	Pryor et al method of risk assessment Intermediate risk:100% Symptomatic: 100% Suspected CAD: 100%	Inclusion •Evaluated for chest pain symptoms due to CAD Exclusion •Previous revasc. •Cardiomyopathy •Valvular heart disease	SPECT •Thallium-201 •Bruce protocol for stress test •Gating: NR •AC: no	N/A	Referred to ICA: Group 1: 100% Group 2:20% No CAD: Group 1: 33% Group 2:18%(among those referred to ICA) (p<0.0001)	NR	Poor No masking mentioned; pre-test likelihood higher in group 1 and prevalence of multivessel disease higher in Group 2, no adjustment for confounding done	
Schaap J (2013) Design: Cohort (Same cohort, multiple tests) Setting: Hospital, Inpatient/ Outpatient: NR	SPECT/CCTA SPECT and ICA	n=107 Mean age: 62.8 ± 10 Male: 69.2% HTN: 63.6% Diabetes: 16.8% Family history: 60.7%	Pre-test likelihood by Diamond & Forrester criteria Median: 87% (22-95% Intermediate: 43.0% High: 52.3% Unknown: 4.7%	Inclusion: • Intermediate - high pre-test likelihood of CAD • Stable anginal complaints Exclusion: • History of CABG/PCI • Unstable cardiac condition • Cardiac rhythm other than sinus rhythm	SPECT/CCTA/CA: • Day 1: stress SPECT (w/ technetium-99m sestamibi) and CCTA • Within 14 days, ICA (femoral or radial access) done • Rest SPECT preceded ICA on same day SPECT/CCTA Technology: • Hybrid system, CardioMD gamma camera and Brilliance 64-slice CT scanner • SPECT, gating: yes • SPECT, AC: yes • Significant disease: >50% stenosis on CCTA • Visual analysis	• Two panel evaluations done: 1) Clinical data w/SPECT/CCTA; 2) Clinical data w/ SPECT/CA • Decision for revascularization made • Decision for PCI vs. CABG made • Panel composition: 1 cardiothoracic surgeon, 2 interventional cardiologists	Primary outcome: Agreement on necessity for revascularization Results: • Overall agreement b/w SPECT/CCTA vs. SPECT and ICA: 92% Secondary outcome: Agreement on PCI vs. CABG Results: • Overall agreement b/w SPECT/CCTA vs. SPECT and CA: 74%	NR	N/A	Data available for outcomes based on 2x2 tables SPECT/CCTA data interpretation done by consensus by 2 experienced physicians blinded to other imaging procedures Average effective radiation dose calculated: CCTA: 4.2 ± 1.0 mSv SPECT: 6.8 ± 2.4 mSv Hybrid SPECT/CCTA: 11.1 ± 2.8 mSv ICA: 10.5 ± 4.9 mSv Mean total effective dose per patient: 21.7 ± 6.4 mSv Mean total effective dose per patient: 21.7 ± 6.4 mSv

ICA: Invasive coronary angiography; SPECT: Single photon emission computed tomography; SD: Standard deviation; HTN: Hypertension; CAD: Coronary artery disease; AC: Attenuation correction; NS: Not significant; NR: Not reported; CCTA: Coronary computed tomography angiography; ; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; N: Number; N/A: Not applicable; CT: Computed tomography

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Symptomatic, High Risk										
Sabharwal NK (2007) Design: Randomized trial (Multiple tested groups) Setting: Hospital chest pain clinic	ETT: SPECT: • Tc-99m sestamibi •Exercise, dipyridamole, or dobutamine stress Follow-up: 24 months	Total n = 457 ETT: n=207 Mean (SD) age: 58.9 (11.4) Male: 57.5% Family history: 46.3% Mean (SD) BMI: 27.6 (4.6) Diabetes: 14.5% Exercise MPI: n=250 Mean (SD) age: 59.7 (12.2) Male: 55.6% Family history: 43.3% Current smoker: 12.8% HTN: 53.2% Mean (SD) BMI: 26.9 (4.5) Diabetes: 19.2%	Pre-test likelihood by ACC/AHA guidelines Pretest likelihood: • Low: 11% • Intermediate: 71% • High: 18% Symptomatic: 100% Suspected CAD: 100%	Inclusion: • Age >25 • Suspected CAD Exclusion: • Acute coronary syndromes • Known CAD • Pregnant or lactating • Abnormal resting EKG	ETT: • Symptom-limited or modified Bruce protocol • Blood pressure, 12-lead EKG monitoring Exercise MPI: • Tc-99m sestamibi •Exercise, dipyridamole, or dobutamine stress •Stress/rest protocol (if stress test abnormal) • Gating: Yes • AC: NR • Semiquantitative visual interpretation	N/A	Referral to other imaging (Incl. ICA) ETT:71% MPI:16% (p<0.0001) Referral to ICA ETT:47% MPI:16% (p<0.0001)	NR	Fair No masking	Equivocal Treadmill test ETT:39% SPECT:14% 1 cardiac death in ETT arm
Pazhenkottil AP (2011) Design: Cohort (Same cohort, multiple tests) Setting: NR	Agreement of image results from SPECT CCTA	n=318 Mean(SD)age:61(11) Males:67% Diabetes:14% HTN: 56% Family history: 27%	Diamond Forrester Method Low Risk: 10% Intermediate risk:73% High risk: 17% Symptomatic: 18% Known CAD:21%	NR	SPECT •Single day protocol •99M-Tc Tetrofosmin •Adenosine stress •Dual head gamma camera (Millenium VG and Hawkeye or Ventri) •Gating:NR •AC: yes CCTA •64-Slice CT scanner (LightSpeed VCT) •iv metoprolol to stabilize HR Images fused on Advantage Workstation 4.3	Fused SPECT/CCTA results used by physician to make decisions regarding ICA or conservative treatment Matched results: reversible defect on SPECT + CCTA showing ≥50% narrowing of coronary luminal diameter Unmatched: Unmatched finding from SPECT and/ or CCTA	ref to ICA (matched):61% ref to ICA (unmatched):20%	NR	N/A	Effective radiation dose for SPECT:10.1±0.1 mSv Estimated radiation dose for CCTA:17.9±5.8 mSv Prospectively triggered CCTA effective radiation dose:1.9±0.5 mSv (n=70)

ETT: Exercise treadmill test; SPECT: Single photon emission computed tomography; PET: Positron emission tomography; CCTA: Coronary computed tomography angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; CT: Computed tomography; CAD: Coronary artery disease; ICA: Invasive coronary angiography; NS: Not significant; N: Number; N/A: Not applicable; MPI: Myocardial perfusion imaging; ACC: American College of Cardiology; AHA: American Heart Association; EKG: Electrocardiogram; AC: Attenuation correction; HR: Heart rate

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Hachamovitch R (2012) Design: Prospective registry design (Multiple tested groups) Setting: 41 different centers	SPECT PET CCTA Follow-up:90 days	Total n= 1,703 Mean (SD)age:62(11) Male:48% Caucasian:82% BMI(kg/m2):31±7 Diabetes:29% HTN:64% SPECT n=565 Mean (SD) age:60(11) Male:49% White:68% BMI(kg/m2):30±7 Diabetes:31% HTN:66% Family History:29% PET	Pre-test likelihood by ACC/AHA guidelines Intermediate to high likelihood=100% Asymptomatic :11% Suspected CAD: 100%	Inclusion •Clinically referred stress SPECT, stress PET, CCTA and PET-CT •Intermediate to high pre-test likelihood of CAD based on ACC/AHA stable angina guidelines Exclusion •Low pre-test likelihood of CAD •Major concomitant non-cardiac disease •Cardiac myopathy •Chest pain at rest within 48 hours of index test	Each study center followed own protocol for imaging	N/A	Referral to cath within 90 days: SPECT: 4.3% PET:11.1% CCTA:13.2% (p<0.001) Change in frequency of medication Aspirin Baseline:44.9% 90 days:56% (p<0.05) Beta-blocker Baseline:32.5 90 days:37.8 (p<0.05)	NR	Good Open-label multi-center study;CAD results interpreted by 2 independent readers	Lost to follow-up:0.3% Withdrew consent: 0.5%
		n=548 Mean (SD)age:63(11) (p<0.05 vs. SPECT) Male:41% (p<0.05 vs. SPECT) White:80% (p<0.05 vs. SPECT) BMI(kg/m2):34±10 (p<0.05 vs. SPECT) Diabetes:41% (p<0.05 vs. SPECT) HTN:73% (p<0.05 vs. SPECT) Family History:24% (p<0.05 vs. SPECT) CCTA n=590 Mean (SD) age:58±11.4 Male:52% White:87% BMI(kg/m2):29±6 Diabetes:16% HTN:56% Family History:37% (p<0.05 vs. SPECT)					Lipid-lowering agent Baseline:48.9 90 days:58.7 (p<0.05) Change in frequency of medication (for moderate or severely abnormal imaging results) Aspirin Before:0.58 After:0.76 (p=0.0002) Beta-Blocker Before:0.42 After:0.58 (p<0.0001)			

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; CCTA: Coronary computed tomography angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; CT: Computed tomography; CAD: Coronary artery disease; N/A: Not applicable; Number; ACC: American College of Cardiology; AHA: American Heart Association

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Known CAD										
Eisenberg MJ (2006) Design: Cohort (multiple tested groups) Setting: Clinical centers in 6 countries	Selective Testing: First stress test post CABG due to clinical indication or no test.(24% AT 12 mo.) Routine Testing: First stress test post CABG as routine test(76% at 12 mo.) Follow-up:12 months	Total n=408 Included in analysis=395 Selective Testing Mean(SD) age:62.9(10.4) Male:77.5% Diabetes:29.9% HTN:63.7% Routine Testing Mean (SD)age:62.6(9.9) Male:87.4% Diabetes:23.4% HTN:61.3%	High risk patients (All had CABG) Symptomatic: NR Known CAD=100%	Inclusion •First successful isolated CABG Exclusion •Valve surgery or aortic repair •Contraindications to repeat cardiac procedures •Future revasc. •Medical condition with prognosis of <1 yr	Each study center followed own protocol for imaging ETT: 65% Stress Perfusion Imaging: 17% Stress Echo: 13% Other Tests(eg. PET):5%	N/A	% patients with second nuclear test: 0.5% Total no. of additional nuclear tests:0.5% Multi-variate analysis: •Center A Odds Ratio:16.94 95% CI:4.33-66.33 p-value:<0.0001 •Men Odds Ratio:2.40 95% CI:1.15-5.03 p-value:0.020 •Center N Odds Ratio:0.24 95% CI:0.11-0.51 p-value:0.0002 •Insulin at discharge Odds Ratio:0.19 95% CI:0.05-0.69 p-value:0.012 •Center M Odds Ratio:0.15 95% CI:0.04-0.49 p-value:0.002 •Center O Odds Ratio:0.04 95% CI:0.01-0.33 p-value:0.002	NR	Fair Masking of outcome assessment NR	Lost to follow-up:2.4% Early death after CABG: 0.7%

CABG: Coronary artery bypass grafting; SD: Standard deviation; CAD: Coronary artery disease; ETT: Exercise treadmill test, Echo: Echocardiography; PET: Positron emission tomography; CI: Confidence interval; NR: Not reported; N: Number; N/A: Not applicable; HTN: Hypertension

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Siegrist PT (2008) Design: Prospective Cohort (Same cohort, multiple strategies tested) Setting: NR	Patient management before PET results Patient management after PET results	n= 100 Mean (SD)age:60.9(12) Male:72% Previous CABG:44% Previous PCI:45%	Risk: NR Symptomatic: NR Known CAD:79% Suspected CAD:8% Suspected small-vessel disease: 13%	NR	PET •Discovery LS PET CT scanner (GE Healthcare) •13 N-Ammonia •Adenosine •Gating: NR •AC: yes	N/A	% patients referred to ICA Decision Before PET results:62 Decision after PET:0 % patients referred to PCI Decision Before PET results:6 Decision after PET:20 % patients referred to CABG Decision Before PET:3 Decision after PET:3 % patients referred for Transplant Decision Before PET:1 Decision after PET:1	NR	N/A	
							% patients referred to Med therapy Decision Before PET:15 Decision after PET:58 No treatment After PET:18 Patient management influenced in 78% population			

PET: Positron emission tomography; N/A: Not applicable; CAD: Coronary artery disease; NR: Not reported; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; N: Number; SD: Standard deviation; AC: Attenuation correction; CT: Computed tomography; ICA: Invasive coronary angiography

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Mixed Risk										
Sharples L (2007) Design: Randomized Trial (Multiple tested groups) Setting: Tertiary cardiothoracic referral center	SPECT MRI stress-ECHO ICA (controls) Follow up:18 months	SPECT Mean(SD) age:62.1(9.5) Males:70% Mean BMI:27.3±4.3 Family history of CAD:8% Treated HTN: 59% MRI Mean (SD)age:62.2(9) Males:68% Mean BMI:28±4.4 Family history of CAD:9% Treated HTN: 51% stress-ECHO Mean (SD)age:61.9(9.9) Males:71% Mean BMI:27.9±4.2 Family history of CAD:10% Treated HTN: 57% ICA Mean age:60.7±9.1 Males:67% Mean BMI:27.6±4.2 Family history of CAD:27% Treated HTN:53%	Pryor Risk assessment High: 69% in all groups Symptomatic:% NR Known CAD: 27%	Inclusion: •Known or suspected CAD, referred for ICA and ETT results indicate referral to ICA Exclusion: •MI<3 months •Functional test <12 months •UA or urgent revascularization •Physically unable to perform ETT •Not available by telephone	SPECT •Two day rest-stress protocol •Adenosine •Gating: When available •AC: NR MRI •1.5-t MAGNET SYSTEM (Signa CV/I, GE Medical Systems) •Stress-rest protocol •Adenosine stress-ECHO •Standard protocol increasing dobutamine dose at 3 minutes duration •Intravenous ultrasound contrast(microspheres) ICA stem or 70% stenosis in any other major vessel=significant CAD •Seldingers technique; femoral route	N/A	Referral to ICA SPECT:88% MRI:80% stress-ECHO:75%	SPECT: No adverse events during test MRI: Arrhythmia: 2 (0.008%)patients Echo: Administration error:1 (0.004%)patient Failed test (due to inadequate achievement of stress, HTN, obesity or arrhythmia): 8 (0.035%) patients	Fair Patients, clinicians, technicians and research assistants not blinded to group allocation	Equivocal results SPECT:6% (p=0.05 vs. ICA) MRI:22%% (p<0.001 vs. ICA) stress-ECHO:10% (p<0.001 vs. ICA) ICA:2%

ETT: Exercise treadmill test; MRI: Magnetic resonance imaging; ICA: Invasive coronary angiography; CAD: Coronary artery disease; NR: Not reported; PCI: Percutaneous coronary intervention; MI: myocardial infarction; SPECT: Single photon emission computed tomography; HTN: Hypertension, BMI: Body mass index; ECHO: Echo cardiography; AC: Attenuation correction; N: Number; N/A: Not applicable; SD: Standard deviation; UA: Unstable angina

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Merhige M (2007) Design: Cohort (Multiple tested groups) Setting: Outpatient	SPECT •99.Tc-Sestamibi PET •Rubidium-82 Follow-up:1year	SPECT n=102 Median age:62±11 Male:54% PET n=2,159 Median age:66±8 Male:54%	Risk: NR Symptomatic: NR Known CAD: SPECT: 44% PET: 49%	Inclusion: •Patients with moderate pre-test likelihood of CAD in PET arm Exclusion: •Patients with pretest likelihood <0.11 or >0.70 (CADENZA computer program)	SPECT •One-day or two-day protocol •Dual-headed gamma camera(CardiaL;ElScint) •Gating: Yes •AC: NR PET •HZL/R camera •Gating: NR •AC: Yes	N/A	Frequency of False Positive acc to ICA SPECT: 15.6% PET: 5.2% (p<0.0001) Reduction in referral to ICA: >50% (p<0.0001 for PET vs. SPECT)	NR	Good Image interpretation done independent of clinical data	
Abdoul-Enein F (2003) Design: Retrospective Cohort (multiple tested groups) Setting: Inpatient and Outpatient (PARR-2 Trial)	Rest group •Group with stress test cancelled due to unexpected perfusion defect •Dual isotope rest Thallium-201/stress Tc-99, sestamibi Stress group •Dual isotope rest Thallium-201/stress Tc-99, sestamibi •Adenosine	Rest Group n= 139 Mean (SD)age: 72(12.6) Male: 72.7% Diabetes: 10.8% HTN: 19.4% Inpatients: 72.7% Stress Group n= 3565 Mean(SD) age: 69.3(10.9) (p=0.01) Male: 65% (p=NS) Diabetes: 21% (p=0.005) HTN: 55% (p<.001) Inpatients: 33% (p<.001)	CADENZA computer program calculated risk Risk stratification:NR Symptomatic Rest group:51.1% Stress group: 45.4%	Inclusion: •No MI •No CABG •Stress test cancelled due to unexpected resting PD (for rest group) •ICA within 3 months after SPECT Exclusion •ICA within 6 months before study	SPECT •Rest images before stress •Same day rest/stress protocol •Patients with nonreversible defects:Tl redistribution 24 hrs after stress study •Siemens Orbiter camera •Bruce protocol for exercise stress •Gating: when available •AC: no ICA: •Femoral route •Any 1 of 3 major coronary arteries show: Stenosis ≥ 70% = significant disease Stenosis ≥ 90% = critical disease	N/A	Referral to ICA: •Rest Group:43.2% •Stress group:19.8% (p<.0001) Hospitalization based on results of SPECT (Rest group only):60.5% Of these, % referred for ICA:73.9% No Hospitalization based on results of SPECT (Rest group only): 39.5% Of these, % underwent ICA within 3 mo.:6.7%	NR	Poor Masking of outcome assessment not mentioned; No adjustment for confounders	
Muzzarelli S (2010) Design: Retrospective Cohort (same cohort, multiple tests) Setting: NR	3 Algorithms for referral to cath •ET based risk stratification and cath if duke score is intermediate or high risk •SPECT based risk stratification,cath if SDS≥8 •ET first, if intermediate Duke risk score then SPECT. Cath if SDS≥8 or high risk Duke-score •Hypothetical referral rates obtained applying algorithms mentioned above	n=955 Mean(SD) age: 61(11) Male:60% BMI (SD):27.5(4.6) Diabetes:23% HTN:63% Family history: 32%	Duke treadmill test Risk: Low: 4% Intermediate: 86% High: 10% Symptomatic Typical Angina:23% Atypical Angina: 32% Dyspnea: 34% Known CAD:43%	Inclusion •Patients referred for CAD evaluation and able to exercise Exclusion •LBBB on baseline ECG •ST segment depression ≥1mm	ETT •Standard, symptom limited bicycle exercise test SPECT •Rest/stress protocol •Gating: yes •AC: NR •Dual-isotope Thallium-201/tc-99m sestamibi	N/A	Patient with known CAD hypothetical referral to ICA ET:27% SPECT:13% (p-value:<0.01) ET + SPECT:12% (p-value:<0.01 vs. ET alone) Patients without known CAD hypothetical referral to ICA: ET:21% SPECT:11% (p-value:<0.01) ET + SPECT:10% (p-value:0.01)	NR	N/A	

ET: Exercise stress test; SPECT: Single photon emission computed tomography; BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; LBBB: Left bundle branch block; ECG: Electrocardiogram; ETT: Exercise treadmill test; NR: Not reported; AC: Attenuation correction; ICA: Invasive coronary angiography; PET: Positron emission tomography; N: Number; SD: Standard deviation; NS: Not significant; SDS: Summed difference score

Table C2. Influence of cardiovascular imaging on decision-making and downstream testing, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol Follow-up	Treatment Protocol	Outcomes Assessed Main Findings	Harms	Quality Evaluation	Notes
Fietcher M (2012) Design: Prospective Cohort (same cohort, multiple tests) Setting: NR	SPECT/CCTA •Tc-99m Tetrofosmin •Dobutamine or adenosine ICA •Stenosis>50% = CAD Matched image: reversible defect on SPECT and stenosis≥50% No match: Normal images or unmatched findings between SPECT and/ or CCTA	n= 62 Mean (SD)age:62(10) Male:76% Mean (SD)BMI: 28(5) Diabetes:16% HTN:68% Family history CAD:35%	Risk: NR Known or suspected CAD Asymptomatic: 50%	Inclusion: •Patients referred for assessment of known or suspected CAD using same day CZT MPI and CCTA Exclusion •Prior CABG	SPECT/CCTA Hybrid •Same day protocol •Single session hybrid scan •CZT/64 slice hybrid camera •Gating: NR •AC: yes •Images fused on Advantage Workstation	N/A	Overall ICA rate= 43% -ICA referral Matched:100% Unmatched:13% (p<0.001)	NR	N/A	

SPECT: Single photon emission computed tomography; CCTA: Coronary computed tomography angiography; HTN: Hypertension; SD: Standard deviation; NR: Not reported; CAD: Coronary artery disease; AC: Attenuation correction; MI: Myocardial infarction; CABG: Coronary artery bypass grafting ; PD: Perfusion defect; ICA: Invasive coronary angiography; N/A: Not applicable; N: Number; BMI: Body mass index

Table C3. Quality of life in patients with cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Symptomatic, Low-Intermediate Risk								
Shaw LJ (2011) Design: Randomized trial (Multiple tested groups) Setting: 43 cardiology practices	ETT SPECT w/multiple procedures • Tc-99m tetrofosmin • Thallium • No pharmacologic stressor used Follow-up: 24 months	Total n = 772 ETT: n:388 Median age: 63 (60,69) Female: 100% BMI: 27.4 (24.2, 30.9) Family history: 47.3% HTN: 55.2% Diabetes: 12.6% Exercise MPI: n=384 Median age: 62 (58,68) Female: 100% BMI: 27.4 (24.6, 31.8) Family history: 45.8% HTN: 52.0% Diabetes: 14.2%	Pre-test likelihood by ACC/AHA guidelines Intermediate risk: 100% Symptomatic :100% Suspected CAD: 100%	Inclusion: • Typical/atypical chest pain or ischemic equivalents (e.g. dyspnea) • Interpretable baseline ECG • Age ≥40 years or postmenopausal • Capable of performing ≥5 metabolic equivalents on the DASI questionnaire • Intermediate pre-test likelihood of CAD Exclusion: • Known CAD (history of MI or catheterization w/a >50% lesion in ≥1 coronary artery • ≤5 metabolic equivalents on the DASI • Pregnant/nursing women • Nuclear medicine study w/in 10 days of study • Electrocardiographic abnormalities such as LBBB, ventricular pacemaker • Significant valvular disease (e.g. severe aortic stenosis) • Uncontrolled HTN (>210/110 mmHg) • Hypotension (<90/60 mmHg) • History of heart failure • LVEF <50% • Patients receiving digoxin therapy	ETT: • Standard or modified Bruce protocol • Blood pressure, 12-lead ECG monitoring SPECT: • 3 potential protocols w/Tc-99m: 1) Rest-thallium/stress-tetrofosmin 2) 2-day tetrofosmin 3) 1-day tetrofosmin (rest/stress sequence) • Gating: when possible • AC: advised, but optional • Visual scoring w/aid of quantitative programs	General QoL Characteristics ETT Excellent:15.4% Very Good:38.8% Good:35.8% Fair:8.5% Poor:1.5% stress-SPECT Excellent:11.4% Very Good:38.1% Good:37.4% Fair:12.1% Poor:1% Life Satisfaction ETT Best:30.9% Average:15.7% Worst:2% SPECT Best:32.6% Average:14.6% Worst:2.3% (All p values >0.20) No significant difference between ETT and SPECT when SAQ subscales were compared	Poor No Intent to treat analysis done	ECG/SPECT interpretation conducted by site investigators Evaluation of angina symptoms by SAQ Average ionizing radiation during SPECT: 14 mSv • Dual-isotope: 24 mSv • Rest/stress 10 mSv

ETT: Exercise treadmill test; SPECT: Single photon emission computed tomography; ECG: Electrocardiogram; SD: Standard deviation;HTN: Hypertension; BMI: Body mass index; CAD: Coronary artery disease; DASI: Duke activity status index; LVEF: Left ventricular ejection fraction; AC: Attenuation correction; MACE: Major adverse cardiovascular event; CP: Chest pain; SAQ: Seattle angina questionnaire; MPI: Myocardial perfusion imaging; ACC: American College of Cardiology; AHA: American Heart Association; N: Number; LBBB: Left bundle branch block; QoL: Quality of life

Table C3. Quality of life in patients with cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Mixed Risk								
Sharples L (2007) Design: Randomized Trial (Multiple tested groups) Setting: Tertiary cardiothoracic referral center	SPECT MRI stress-ECHO ICA (controls) Follow up:18 months	SPECT n=224 Mean age:62.1±9.5 Males:70% Mean BMI:27.3±4.3 Family history of CAD:8% Treated HTN: 59% MRI n=226 Mean age:62.2±9 Males:68% Mean BMI:28±4.4 Family history of CAD:9% Treated HTN: 57% stress-ECHO n=226 Mean age:61.9±9.9 Males:71% Mean BMI:27.9±4.2 Family history of CAD:10% CAD:10% ICA n=222 Mean age:60.7±9.1 Males:67% Mean BMI:27.6±4.2 Family history of CAD:27% Treated HTN:53%	Pryor Risk assessment High: 69% in all groups Symptomatic:% NR Known CAD:NR	Inclusion: •Known or suspected CAD, referred for ICA and ETT results indicate referral to ICA Exclusion: •MI<3 months •Functional test <12 months •UA or urgent revascularization •Physically unable to perform ETT •Not available by telephone	SPECT •Two day rest-stress protocol •Adenosine •Gating: When available •AC: NR MRI •1.5-t MAGNET SYSTEM (Signa CV/I, GE Medical Systems) •Stress-rest protocol •Adenosine stress-ECHO •Standard protocol increasing dobutamine dose at 3 minutes duration •Intravenous ultrasound contrast(microspheres) ICA •50% stenosis in left main stem or 70% stenosis in any other major vessel=significant CAD •Seldingers technique; femoral route	Mean difference in SAQ scores SPECT At 18 months: Exertional Capacity Scale: 2 Anginal Stability Scale: 1.9 Anginal Frequency Scale: -2.6 Treatment Satisfaction Scale: 0.3 Disease Perception Scale: 0.0 MRI At 18 months: Exertional Capacity Scale: 2 Anginal Stability Scale: 3.2 Anginal Frequency Scale: -0.8 Treatment Satisfaction Scale: 0.1 Disease Perception Scale: -0.3 stress-ECHO At 18 months: Exertional Capacity Scale: -0.5 Anginal Stability Scale: 0.1 Anginal Frequency Scale: -3.2 Treatment Satisfaction Scale: 0.3 Disease Perception Scale: -1.6 (p=NS, all positive values in favor of angiography) Adjusting for baseline by treatment group, exercise capacity score significantly higher in SPECT medically managed group vs. others(p<0.05)	Fair	Equivocal results SPECT:6% (p=0.05 vs. ICA) MRI:22%% (p<0.001 vs. ICA) stress-ECHO:10% (p<0.001 vs. ICA) ICA:2%

SPECT: Single photon emission computed tomography; MRI: Magnetic Resonance Imaging; ECHO: Echocardiography; ICA: Invasive coronary angiography; SD: Standard deviation; BMI: Body mass index; HTN: Hypertension; NR: Not reported; CAD: Coronary artery disease; ETT: Exercise treadmill testing; MI: Myocardial infarction; UA: Unstable angina; AC: Attenuation correction; CABG: Coronary artery bypass grafting; PCI: Percutaneous Coronary Intervention; SAQ: Seattle angina questionnaire; N: Number; NS: Not significant

Table C3. Quality of life in patients with cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Sharples L (2007), Cont. Design: Randomized Trial (Multiple tested groups) Setting: Tertiary cardiothoracic referral center						Mean SF-36 physical and mental scores ICA Physical component Score:43.6 Mental Component Score:52.0 SPECT Physical Component Score:43.2 Mental Component Score:52.2 MRI Physical Component Score:41.8 Mental Component Score:50.8 stress-ECHO Physical Component Score:44.5 Mental Component Score:53.5 (p=NS) When adjusted for baseline by treatment group, no significant difference between groups for SF-36 scores and EuroQoL scores		

SPECT: Single photon emission computed tomography; MRI: Magnetic Resonance Imaging; ECHO: Echocardiography; ICA: Invasive coronary angiography; NS: Not significant

Table C4. Diagnostic accuracy of myocardial perfusion imaging

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Test Protocol	Outcomes Assessed Main Findings		Harms	Notes
Danand I (2013) Design: Cohort Setting: NR	PET •Oxygen-15 water •Adenosine CTCA ICA (Gold standard)	n=120 Mean Age:61±10 Male:64% Mean BMI:28±4 kg/m^2 HTN:56% Diabetes:21% Family History:51%	Suspected CAD:100% Elevated risk for CAD(Presence of two or more risk factors)	Inclusion: • Stable angina or elevated risk for CAD (presence of two or more risk factors) Exclusion: • Atrial Fibrillation •Atrioventricular block; second or third degree •Impaired renal function •Symptomatic asthma •Pregnancy •Documented history of CAD	PET •Rest-stress protocol •Gating: NR •AC: Yes •MBF analyzed using Cardiac VUer software CTCA •Oral or iv metoprolol to stabilize HR •3-D workstation (Brilliance; Philips Medical systems) •CTCA performed after CAC scoring	MBF as perfusion parameter •PET/CTCA TP=37 TN=65 FP=6 FN=12 •PET TP=37 TN=59 FP=12 FN=12	 Sensitivity:76% Specificity:92% PPV:86% NPV:84% Sensitivity:76% Specificity:83% PPV:76% NPV:83%	NR	PET and CTCA readers were masked to ICA results
					ICA •Degree stenosis(≥50% considered significant) and/or FFR (≤0.80 considered significant)	•CTCA TP=49 TN=24 FP=47 FN=0	Sensitivity:100% Specificity:34% PPV:51% NPV:100%		
						CFR as perfusion parameter •PET/CTCA TP=37 TN=54 FP=17 FN=12	 Sensitivity:76% Specificity:76% PPV:69% NPV:82%		
						•PET TP=37 TN=45 FP=26 FN=12 •CTCA TP=49 TN=24 FP=47 FN=0	Sensitivity:76% Specificity:63% PPV:59% NPV:79% Sensitivity:100% Specificity:34% PPV:51% NPV:100%		

CTCA: Computed tomography coronary angiography; PET: Positron emission tomography; ICA: Invasive coronary angiography; HTN: Hypertension; CAD: Coronary artery disease; NR: Not reported: AC: Attenuation correction; HR: Heart Rate: FFR: Fractional flow reserve; TP: True positive; TN: True negative; FP: False positive; FN: False negative; CFR: Coronary flow reserve; PPV: Positive predictive value; NPV: Negative predictive value; N: Number; BMI: Body mass index: MBF: Myocardial blood flow; HR: Heart rate

Table C4. Diagnostic accuracy of myocardial perfusion imaging

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Test Protocol	Outcomes Assessed Main Findings		Harms	Notes
De Bruyne B (2001) Design: Prospective Cohort Setting: Hospital, Inpatient/ Outpatient: NR	SPECT •^{99m} Tc Sestamibi •Adenosine ICA (Gold standard)	n=57 Mean Age: 61±11 Male: 77% BMI: NR HTN: 25% Diabetes: 7%	Known CAD:100%	Inclusion: •Documented MI ≤ 6 days before the study •No totally akinetic territory •Normally contracting regions other than that of prior MI •Angioplasty scheduled for infarct related artery only •Stenosis ≥2.5mm	SPECT: • 2-day stress/rest protocol • 2-headed cameras (Vertex Epic dual head ADAC gamma camera) • Gating: yes, at rest • AC: NR • Semi-quantitative 4 scale scoring on 16 -segment model FFR-PCI: • Femoral route •FFR<0.75 = positive ischemia	•TP=39 TN=58 FP=8 FN=9	Sensitivity:82% Specificity:87% PPV:81% NPV:91%	NR	
Kajander S. (2010) Design: Prospective cohort Setting: Outpatient	PET •^{15}O-labeled water •Adenosine PET/CT ICA (Gold standard) •Luminal diameter >50% / FFR<0.8 considered significant CT	n = 107 Mean age: 63.6± 7 Male: 61% Single-vessel:13% Multi-vessel:23% Diabetes: 14% Hypertension: 41%	Suspected CAD: 100% 30% to 70% pre-test likelihood of CAD	Inclusion criteria: •History of stable chest pain •30-70% pre-test likelihood of CAD Exclusion criteria: •Atrial fibrillation •Unstable angina •second or third degree atrioventricular block •Severe CHF •Symptomatic asthma •Pregnancy	PET imaging: •Rest-stress perfusion protocol used •64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems) •Gating: no • AC: NR PET/CT imaging: •Rest-stress protocol used •64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems) •Gated:NR •AC: yes	•PET TP=36 TN=60 FP=6 FN=2 •PET/CT TP=36 TN=66 FP=0 FN=2	PET: Sensitivity:95% Specificity:91% PPV :86% NPV:97% Accuracy:92% PET/CT: Sensitivity:95% Specificity:100% PPV:100% NPV:98% Accuracy:98% (accuracy p=0.014 vs. PET)	NR	Average radiation dose: CTA with prospective ECG triggering = 7.6 mSv CTA with retrospective ECG triggering = 19.9 mSv = 1.7 mSv PET/CT with prospective triggering=9.3 mSv
					ICA: • ICA performed on Siemens Axiom Artis Coronary angiography system • Quantitative analysis done using Quantcore CT: •iv metoprolol to stabilize HR •64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems) •Iodinated contrast •Gated: retrospectively in 21 patients				PET/CT with spiral CT=21.8 mSv ICA=7 mSv PET not performed in 3 patients due to technical reasons FFR not performed in 4 patients due to technical and scheduling reasons

SPECT: Single photon emission computed tomography; ICA: Invasive coronary angiography; BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; MI: Myocardial infarction; AC: Attenuation correction; NR: Not reported; FFR: Fractional flow reserve; PCI: Percutaneous coronary intervention; TP: True positive; TN: True negative; FP: False positive; FN: False negative; PPV: Positive predictive value; NPV: Negative predictive value; PET: Positron emission tomography; CT: Computed tomography; CTA: CT coronary angiography; ECG: Electrocardiogram; N: Number; CHF: Congestive heart failure

Table C4. Diagnostic accuracy of myocardial perfusion imaging

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Test Protocol	Outcomes Assessed Main Findings	Harms	Notes
Oraby M.A (2002) Design: Cohort Setting:NR	SPECT •Thallium-201 •Dipyridamole MCE (Gold standard) •Optison: Contrast enhancer(Octafluoropropane-filled albumin microspheres)	n=38 Mean age:66±11 Male:100% Smoker:58% HTN:76% Diabetes:53% Family History:29%	Known or suspected CAD: 100%	Inclusion: •Known or suspected CAD Exclusion: •Sensitivity to blood products •Unstable angina •Recent (<6 weeks) MI •Severe valvular heart disease •Advanced lung disease	SPECT •Stress protocol •Triple-headed rotating gamma camera (Siemens Inc.) •Gating: NR •AC:NR MCE •Sequoia platform (Acuson Corp.,) •Images obtained with patients in	•SPECT TP=14 TN=14 FP=0 FN=10 Sensitivity:58% Specificity:100% PPV:100% NPV:58%	Dipyridamole: •Headaches:5% •Chest pain:7% •Dizziness:5% Optison: •Abnormal taste:5%	
Yanagisawa H (2002) Design: Cohort Setting: Acute clinical setting	SPECT •^{201} Thallium •Dipyridamole ICA (Gold standard)	n=165 Mean age:61±9 Male:83.6% HTN:54% Diabetes:37% Single vessel:75.7% Multi vessel:24.2%	Suspected CAD:100%	Inclusion •165 consecutive patients undergoing ICA and SPECT	SPECT: •Stress protocol •Digital gamma camera used (Prism 2000 XP) •AC:NR •Gating:NR ICA: •Femoral route •FFR<0.75 :indicated functionally important stenosis	Diabetes Sensitivity:90% Specificity:70% Accuracy:82% No Diabetes Sensitivity:71% Specificity:74% Accuracy:72% (p<0.05 for patients with diabetes vs. without)	NR	
						Diagnostic accuracy for other subgroups (smoking, hyperlipidemia, multi-vessel disease) p=NS.		
Yanagisawa H (2004) Design: Cohort Setting: NR	SPECT •^{201} Thallium •Adenosine ICA (Gold standard) •Luminal diameter >50%and/ FFR<0.8 considered significant	n=245 Mean age:62±9 Male:84% HTN:65% Diabetes:39% Single vessel:75% Multi vessel:25%	Suspected CAD:100%	Inclusion •245 consecutive patients that had ICA and SPECT between Feb 1997 and Dec 2002	SPECT: •Stress protocol •Digital gamma camera used (Prism 2000 XP) •AC:NR •Gating:NR ICA: •Femoral route •FFR<0.75 :indicated functionally important stenosis	Diabetes Sensitivity:83% Specificity:75% PPV:81% NPV:78% Accuracy:80% No Diabetes Sensitivity:79% Specificity:83% PPV:73% NPV:86% Accuracy:81% (p=NS)	NR	

SPECT: Single photon emission computed tomography; ICA: Invasive coronary angiography; HTN: Hypertension; CAD: Coronary artery disease; AC: Attenuation correction; NR: Not reported; FFR: Fractional flow reserve; PPV: Positive predictive value; NPV: Negative predictive value; N: Number; NS: Not significant; MCE: Myocardial contrast echocardiography; TP: True positive; TN: True negative; FP: False positive; FN: False negative;

Table C4. Diagnostic accuracy of myocardial perfusion imaging

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Test Protocol	Outcomes Assessed Main Findings		Harms	Notes
Kajander S. (2011) Design: Prospective cohort Setting: Outpatient	PET •Oxygen-15 water •Adenosine ICA (Gold standard) •Luminal diameter >50% / FFR<0.8 considered significant	n = 107 Mean age: 63.6± 7 Male: 61% Single-vessel:13% Multi-vessel:23% Diabetes: 14% Hypertension: 41% (Same patient population as Kajander S.-2010)	Suspected CAD:100% 30-70% Pre-test likelihood of CAD	Inclusion criteria: •History of stable chest pain •30-70% pre-test likelihood of CAD Exclusion criteria: •Atrial fibrillation •Unstable angina •second or third degree atrioventricular block •Severe CHF •Symptomatic asthma •Pregnancy	PET imaging: •Rest-stress perfusion protocol used •64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems) •Gating: no • AC: NR ICA: • ICA performed on Siemens Axiom Artis Coronary angiography system • Quantitative analysis done using Quantcore	Analysis of quantitative blood flow: TP=36 TN=60 FP=6 FN=2 Analysis of relative uptake of tracer(as measure of perfusion): TP=28 TN=48 FP=18 FN=10	Sensitivity:95% Specificity:91% PPV:86% NPV:97% Sensitivity:74% Specificity:73% PPV:61% NPV:83%		PET not performed in 3 patients due to technical reasons FFR not performed in 4 patients due to technical and scheduling reasons
Melikian N (2010) Design: Cohort Setting: NR	SPECT • Tc-99m sestamibi • Adenosine ICA (Gold standard) Fractional flow reserve (FFR)-guided PCI	n=67 Mean Age: 64 ± 10 Male: 62% BMI: 27.6 ± 4.6 2-vessel disease: 52.2% 3-vessel disease: 47.8% HTN: 54% Diabetes: 19% Family history: 43%	Known CAD: 100%	Inclusion: • Stable angina w/angiographic evidence of ≥2 vessel CAD (≥50% stenosis) Exclusion: • Recent ACS • Confirmed old MI • Previous CABG • Left main stem artery stenosis • Left ventricular systolic function <50% and/or LV regional wall motion abnormality • Arrhythmia • Poorly controlled airway disease	SPECT: • 2-day stress/rest protocol • 2-headed cameras (Philips Adac Vertex and Cardio MD) • Gating: yes • AC: no • Visual and semi-quantitative (AHA) scoring FFR-PCI: • Femoral route • FFR<0.80 = positive ischemia • Measured in all 3 main coronary vessels	•SPECT TP: 31 TN: 10 FP: 10 FN: 16	Sensitivity: 66% Specificity: 50%		Consensus scoring of SPECT done by experienced nuclear physicians blinded to angiographic (w/the exception of coronary dominance) and FFR data

SPECT: Single photon emission computed tomography; ICA: Invasive coronary angiography; BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; MI: Myocardial infarction; AC: Attenuation correction; NR: Not reported; FFR: Fractional flow reserve; PCI: percutaneous coronary intervention; TP: True positive; TN: True negative; FP: False positive; FN: False negative; PPV: Positive predictive value; NPV: Negative predictive value; PET: Positron emission tomography; CT: Computed tomography; CTA: CT coronary angiography; ECG: Electrocardiogram; N: Number; CHF: Congestive heart failure; LV: Left ventricle

Table C5. Summary evidence table: Risks associated with cardiac nuclear imaging, by stressor agent.

Adverse Effect	Pharmacologic Agent	Study Information	Risk of bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect
Pharmacologic SPECT								
Arrhythmias								
	Adenosine	N=1,459 RCT=1; RXR=1; CS-CTRL=2; SGL-C=1	High	Inconsistent	Direct	Imprecise	++ Low	Association established
	Dobutamine	N=2,750 RCT=1; RXR=1; CS-CTRL=1; CS=2	High	Consistent	Direct	Imprecise	+++ Moderate	Increased effects with dobutamine
	Dipyridamole	N=108 CS-CTRL=1	High	N/A	Direct	N/A	+ Insufficient	No directionality
	Regadenoson	NR	--	--	--	--	--	--
	Binodenoson	N=240 RXR=1	Medium	N/A	Direct	N/A	+ Insufficient	No directionality
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established
Chest Pain								
	Adenosine	N=2,651 RCT=1; RXR=2;CC=1;CS-CTRL=1; SGL-C=1	Medium	Consistent	Direct	Imprecise	+++ Moderate	Strong association with adenosine
	Dobutamine	N=2,296 RCT=1; RXR=1; CS=2	High	Inconsistent	Direct	Imprecise	+ Low	Association established
	Dipyridamole	NR	--	--	--	--	--	--
	Regadenoson	N=514 SGL-C=1	High	N/A	Direct	N/A	+ Insufficient	Association established
	Binodenoson	N=240 RXR=1	Medium	N/A	Direct	N/A	+ Insufficient	Association established
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established
Dyspnea								
	Adenosine	N=2,611 RCT=1; RXR=1; CC=1; CS-CTRL=1; SGL-C=1	Medium	Consistent	Direct	Imprecise	+++ Moderate	Strong association with adenosine
	Dobutamine	N=2,296 RCT=1; RXR=1; CS=2	High	Inconsistent	Direct	Imprecise	+ Low	No directionality

Adverse Effect	Pharmacologic Agent	Study Information	Risk of bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect
	Dipyridamole	NR	--	--	--	--	--	--
	Regadenoson	N=514 SGL-C =1	High	N/A	Direct	N/A	+ Insufficient	Association established
	Binodenoson	N=240 RXR=1	Medium	N/A	Direct	N/A	+ Insufficient	Association established
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established
Flushing/Chills								
	Adenosine	N=2,611 RCT=1; RXR=1; CC=1; CS-CTRL=1; SGL-C=1	Medium	Consistent	Direct	Imprecise	+++ Moderate	Strong association with adenosine
	Dobutamine	N=2,582 RXR=1; CS-CTRL=1; CS=2	High	Inconsistent	Direct	Imprecise	Low	No directionality
	Dipyridamole	NR	--	--	--	--	--	--
	Regadenoson	NR	--	--	--	--	--	--
	Binodenoson	N=240 RXR=1	Medium	N/A	Direct	N/A	+ Insufficient	Association established
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established
Headache/Dizziness								
	Adenosine	N=805 RXR=1; SGL-C=1	Medium	Consistent	Direct	Imprecise	+++ Moderate	Association established
	Dobutamine	N=2,582 RXR=1; CS-CTRL=1; CS=2	High	Consistent	Direct	Imprecise	++ Low	Association established
	Dipyridamole	NR	--	--	--	--	--	--
	Regadenoson	N=514 SGL-C=1	High	N/A	Direct	N/A	+ Insufficient	Association established
	Binodenoson	NR	--	--	--	--	--	--
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established
Changes in Blood Pressure								
	Adenosine	N=597 RXR=1; CC=1; CS-CTRL=1	High	Inconsistent	Direct	Imprecise	++ Low	No directionality

Adverse Effect	Pharmacologic Agent	Study Information	Risk of bias	Consistency	Directness	Precision	Strength of Evidence	Direction of Effect
	Dobutamine	N=1,698 RCT=1; CS=1; CS-CTRL =1	High	Inconsistent	Direct	Imprecise	++ Low	No directionality
	Dipyridamole	N=357 CC=1; CS-CTRL =1	High	Consistent	Direct	Precise	++ Low	No directionality
	Regadenoson	N=514 SGL-C=1	High	N/A	Direct	N/A	+ Insufficient	Association established
	Binodenoson	N=240 RXR=1	Medium	N/A	Direct	N/A	+ Insufficient	No association seen with binodenoson
	Arbutamine	NR	--	--	--	--	--	--
GI Effects/Nausea								
	Adenosine	N=1,859 RCT=1; CC=1	Medium	Consistent	Direct	Precise	++ Low	Association established
	Dobutamine	N=2,582 RXR=1; CS-CTRL =1; CS=2	High	Consistent	Direct	Precise	+++ Moderate	Association established
	Dipyridamole	NR	--	--	--	--	--	--
	Regadenoson	N=514 SGL-C=1	High	N/A	Direct	N/A	+ Insufficient	No directionality
	Binodenoson	NR	--	--	--	--	--	--
	Arbutamine	N=40 RXR=1	High	N/A	Direct	N/A	+ Insufficient	Association established

CC: comparative cohort; CS-CTRL: case control; ETT: exercise treadmill test; GI: gastrointestinal; N: number; N/A: not applicable; RCT: randomized controlled trial; RXR: randomized crossover; SGL-C: single-arm cohort; SPECT: single photon emission computed tomography;

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Symptomatic, High Risk								
Al-Mallah M.H (2010) Design: Case-control (Multiple groups) Setting: NR	Adverse events of adenosine in: Cardiac transplant patients Control group: age-gender matched patients who underwent adenosine SPECT in the same time period, 2:1 ratio Follow-up: 3 yrs (mean)	Total=306 Cardiac Transplant patients n=102 mean age=:59±9 Male:79% African American:15% Diabetes:29% HTN:91% Hyperlipidemia:73% Control patients n=204 mean age=:58±10 Male:80% African American:16% Diabetes:30% HTN:88% Hyperlipidemia:54%(p=0.001)	High risk Symptomatic: 8% Screening purpose: 92% Known vs. Suspected: NR	Inclusion: • Patients who underwent adenosine SPECT between 1997 and 2005	•Rest/stress protocol •Two-headed camera •Gated: yes •AC:NR	•Sinus Pause Transplant:4.9% Control:0% (p= 0.0001) •Dyspnea Transplant:33% Control:59% (p<0.0001) •Flushing Transplant:28% Control:16% (p= 0.021) Termination of adenosine infusion:3.9% Chest pain, 1st degree AV Block p=NS; 3rd degree AV block significantly different b/w groups	N/A	
Elhendy A (1998) Design: Series (Multiple groups) Setting: Imaging Laboratory	No comparator, adverse effects of Dobutamine-SPECT	n= 1076 Mean age= 59±11 yrs Male: 64% Previous MI:50%	High risk Symptomatic :71%	Inclusion •Patients referred for dobutamine stress testing for evaluation of MI between Nov 1990 and March 1997 and had limited exercise capacity Exclusion •Severe HF •Valvular heart disease •Severe HTN •Hypotension Unstable chest pain	•Dobutamine infused at 5 µg/kg/min and then increased by 10 µg/kg/min every 3 mins to 40µg/kg/min •Tc-99m sestamibi or Tetrofosmin or 201-Thallium •One day or two day protocol	Symptoms during the test Atypical Chest pain: 12% Headache:6.5% Dyspnea: 5.8% Flushing: 0.2% Nausea:0.6% Dizziness:4% Anxiety: 2% Chills:5% Symptomatic Hypotension: 0.8% Typical angina:27% Premature atrial contractions:6.3% Premature ventricular contractions:31% Supraventricular tachycardia:3.5% Afib: 1.1% Reasons for termination of test Angina:6.7% ST change:1.1% Arrythmias:1.4% HTN:0.01% Hypotension:2.6% Dyspnea:1.1% Chills, flushing, dizziness, anxiety:0.09%	N/A	

SPECT: Single photon emission computed tomography; HTN: Hypertension; N: Number; NR: Not reported; AC: Attenuation correction; N/A: Not applicable; HF: Heart failure; MI: Myocardial Infarction

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Elhendy A (2000) Design: Case control (Multiple groups) Setting: Imaging Laboratory	Adverse effects of Dobutamine-atropine stress test in ≥70 yrs <70 yrs(matched for gender and previous MI)	n=454 ≥70 yrs n=227 Mean age:75±4 Men: 49% HTN: 47% Diabetes:15% <70 yrs(matched for gender and previous MI) n=227 Mean age:55±11 Men: 49% HTN: 44% Diabetes:17%	High risk Symptoms ≥70 yrs Chest pain:33% Atypical chest pain:36% Dyspnea:10% <70 yrs Chest pain:31% Atypical chest pain:30% Dyspnea:11% Known CAD: 36% in both groups had previous MI	Inclusion •Patients referred for dobutamine stress testing for evaluation of MI between Jan 1994 and Jan 1999 Exclusion •Severe HF •Valvular heart disease •Severe HTN •Hypotension •Unstable chest pain	•Dobutamine infused at 5 µg/kg/min and then increased by 10 µg/kg/min every 3 mins to 40µg/kg/min •Tc-99m sestamibi or Tetrofosmin or 201-Thallium •One day or two day protocol	Symptoms during the test ≥70 yrs Headache:7% Flushing: 0% Nausea:3% Dizziness:4% Anxiety: 2% Chills:7% Symptomatic Hypotension: 1% Typical angina:30% Symptoms during the test <70 yrs Headache:5% Flushing: 0.4% Nausea:6% Dizziness:2% Anxiety: 3% Chills:6% Symptomatic Hypotension: 1% Typical angina:23%	N/A	
						Reasons for termination of test ≥70 yrs Angina:3% ST change:2% Arrythmias:1.3% HTN:0.9% Hypotension:2% Chills, flushing, dizziness, anxiety:0.4% Reasons for termination of test <70 yrs Angina:4% ST change:2% Arrythmias:0.4% HTN:0.4% Hypotension:1% Chills, flushing, dizziness, anxiety:0.4% All differences NS		

MI: Myocardial infarction; HTN: Hypertension; CAD: Coronary artery disease; HF: Heart failure; N: Number; N/A: Not applicable; NS: Not significant

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Hatanaka K (2007) Design: Cohort Setting: Hospital; inpatient/outpatient NR	No comparator, side effects during adenosine infusion studied	n=206 Mean age:68.9±10.5 Men: 51.4% HTN: 62.1% Diabetes:31.6% Currently Smoking: 11.7% Hyperlipidemia: 54.4% Family history of CAD:36.9% Previous MI:18.9% Previous CABG: 5.8% Previous PCI: 31.6%	Risk: NR Symptoms Chest Pain:47.6% Typical chest pain:39.3% Anginal chest pain:8.3% Known CAD: 39.8%	<u>Exclusion</u> •Hypotension •CHF •Greater than first degree AV block •New York heart association class III or IV •COPD or asthma	<u>SPECT</u> •Thallium-201 •Computerized infusion pump for adenosine • Gating and AC: NR	<u>Adverse effects:</u> Chest discomfort Males:37 Females:58 (p<0.05) Chest pain Males:21.7% Females:28% Headache Males:13.2% Females:18% Flushing Males:46.2% Females:49% Palpitation Males:23.6% Females:32% Sore throat, Shortness of breath,Epigastralgia and Tolerance score^ reported, all NS. Frequency of Adverse effects: ≥75 years:65.3% 65-74 years:86.8% ≤64 years:83.3% (p<0.05 for ≥75 years vs. others)	N/A	

HTN: hypertension; CAD: Coronary artery disease; MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: percutaneous transluminal coronary angioplasty; NR: Not reported; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; AC: Attenuation correction; NS: Not significant; N: Number; N/A: Not applicable; N: Number
^: Tolerance Score: range 1-5; 1=no discomfort, 5=severe discomfort

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Known CAD								
Udelson JE (2004) Design: Randomized cross-over trial (multiple testing groups) Setting: NR	Patients randomized to following: Binodenoson SPECT Adenosine SPECT Binodenoson patients further randomized to the following dosing regimens: •0.5µg/kg bolus for 30 seconds •1.0 µg/kg bolus for 30 seconds •1.5 µg/kg bolus for 30 seconds •0.5µg/kg/min for 3 minutes	0.5µg/kg n=61 Mean age:65.8 Males:67% White:84% Mean screening BMI:29.6 1.0µg/kg n=64 Mean age:65.6 Males:62% White:90% Mean screening BMI:32 1.5µg/kg n=58 Mean age:65.3 Males:71% White:88% Mean screening BMI:30.1 1.5µg/kg x 3 mins n=57 Mean age:66.7 Males:55% White:75% Mean screening BMI:30.7	High risk Symptomatic : 100% Known CAD 0.5µg/kg:86% 1.0 µg/kg:97% 1.5 µg/kg:84% 0.5µg/kg/min x 3 mins:91% High likelihood of CAD 0.5µg/kg:10% 1.0 µg/kg:3% 1.5 µg/kg:11% 0.5µg/kg/min x 3 mins:7%	Inclusion •Symptomatic, known CAD or high pretest likelihood of CAD Exclusion •MI or revasc<30 days •Asthma •Bronchospasm •second or third degree AV-block •LVEF≤0.35	SPECT •99m Tc Sestamibi or Th-201 •Adenosine infusion: 140 µg/kg/min for 6 min •Binodenoson doses injected into peripheral vein over 30 seconds with isotope injected after 3.5 mins	Any composite objective AE 0.5µg/kg:3% 1.0 µg/kg:0 1.5 µg/kg:4% 1.5µg/kg infusion:4% Adenosine:4% Any composite subjective AE 0.5µg/kg:33% (p<0.001) 1.0 µg/kg:73% (p<0.002) 1.5 µg/kg:72% (p<0.021) 1.5µg/kg infusion:80% Adenosine: 92% Any composite objective or subjective AE 0.5µg/kg:33%(p<0.01) 1.0 µg/kg:73% (p<0.01) 1.5 µg/kg:72% (p<0.01) 1.5µg/kg infusion:80% (p<0.01) Adenosine:92% Binodenoson RR 0.5µg/kg:0.36 1.0 µg/kg:0.8 1.5 µg/kg:0.78 1.5 µg/kg:0.78	Poor No Intent to treat followed	Single-blinded drug administration
		Adenosine patient characteristics: NR				1.5µg/kg infusion:0.87 Atrio ventricular block 0.5µg/kg:0 1.0 µg/kg:0 1.5 µg/kg:0 1.5µg/kg infusion:0 Adenosine:3% (p=0.0075 binodenoson vs. adenosine) VAS for intensity of subjective Adverse events Mean(SD) Composite(0-30) 0.5µg/kg: 1.7(4.14)(p<0.01 vs. adenosine, p<0.01 vs. other doses) 1.0 µg/kg:4.1(3.93)(p<0.01 vs. adenosine, p<0.01 vs. other doses 1.5 µg/kg:5(5.33)(p<0.01 vs. adenosine) 1.5µg/kg infusion:6(5.21)(p<0.01 vs. adenosine) Adenosine:8.8(6.3)		

SPECT: Single photon emission computed tomography; BMI: Body mass index; NR: Not reported; CAD: Coronary artery disease; MI: Myocardial infarction; AV:Atrioventricular; LVEF: Left ventricular ejection fraction; AE: adverse effect, SOB: Shortness of breath, RR: Relative risk; VAS: Visual analog score; SD: Standard deviation; N: Number

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Udelson JE (2004), Cont. Design: Randomized cross-over trial (multiple testing groups)						Chest pain(0-10) 0.5µg/kg:0.6(1.54)(p<0.01 vs. adenosine) 1.0 µg/kg:1.2(1.92)(p<0.01 vs. adenosine) 1.5 µg/kg:2.1(2.63)(p<0.02 vs. adenosine) 1.5µg/kg infusion:1.9(2.50)(p<0.01 vs. adenosine) Adenosine:3.9(3.14) SOB (0-10) 0.5µg/kg:0.7(1.88)(p<0.01 vs. adenosine) 1.0 µg/kg: 2(2.45)(p=0.05 vs. adenosine) 1.5 µg/kg:1.8(2.45)(p<0.02 vs. adenosine) 1.5µg/kg infusion:2.4(2.56) Adenosine:2.8(3.07) Flushing(0-10) 0.5µg/kg:0.5(1.5)(p<0.01 vs. adenosine) 1.0 µg/kg:0.9(1.71)(p<0.01 vs. adenosine) 1.5 µg/kg:1.2(2.05)(p<0.01 vs. adenosine) 1.5µg/kg infusion:1.5(2.43)(p<0.01 vs. adenosine) Adenosine:2.7(3.03)		

SPECT: Single photon emission computed tomography; BMI: Body mass index; NR: Not reported; CAD: Coronary artery disease; MI: Myocardial infarction; AV:Atrioventricular; LVEF: Left ventricular ejection fraction; AE: adverse effect, SOB: Shortness of breath, RR: Relative risk; VAS: Visual analog score; SD: Standard deviation; N: Number

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Holmberg JM (1997) Design: Retrospective Case control Setting: University hospital Outpatient imaging center	Side effects of Dipyridamole Adenosine (Controls): Matched by age, body weight, sex, previous MI, previous CABG or PCI, ratio 2:1	Total n=108 Dipyridamole PET: n=36 Mean (SD) age: 59.3 (12.2) Female: 31% Mean weight (kg): 76.9 (17.1) Ejection fraction: 39.7 (6.2) Prior MI: 94% Prior PTCA: 19% Prior CABG: 36% HTN: 44% Adenosine PET: n=72 Mean (SD) age: 58.9 (10.9) Female: 31% Mean weight (kg): 75.7 (18.3) Ejection fraction: 31.7 (7.5) Prior MI: 94% Prior PTCA: 18% Prior CABG: 33% HTN: 43%	Risk: NR Symptoms:NR All patients with history of CAD (prior MI, revascularization, or both)	Inclusion: •Patients referred for PET from Jan 1993 to March 1996 for CAD evaluation	PET •N-13 Ammonia and F-18 FDG •ECAT-II scanner •Gating: NR •AC: yes	Average no. of side effects per patient Adenosine:1.39±1.12 Dipyridamole:1.08±1.10 p=0.337 No. of patients reporting: ≥1 side effect Adenosine:82% Dipyridamole:67% p=0.047 Late-onset side effects Adenosine:0% Dipyridamole:50% p<0.0001 Prolonged duration side effects(>5 mins) Adenosine:0% Dipyridamole:39% p<0.0001 Side effects requiring medical intervention Adenosine:6% Dipyridamole:53% p<0.0001	Poor Retrospective case-control, ,matching done to control for confounding but baseline LVEF still different between groups	
AlJaroudi WA (2012) Design: Retrospective Cohort (One group receiving multiple tests)	Adverse effects of regadenoson ETT SPECT • Tc-99m tetrofosmin • Regadenoson	n=514 Mean age:60±12 Male:76% White:65% BMI(kg/m^2):30±6 Diabetes: -Insulin dependent:11% -Non-Insulin dependent:19% HTN:81%	Risk: NR Symptoms: Chest pain: 39% Shortness of breath: 32% Known CAD:51%	Inclusion: •Patients who failed to reach THR •Patients with COPD and asthma were not excluded Exclusion: •High degree heart block and no pacemakers	ETT •Bruce or Cornell Protocol • Treadmill speed was dropped by 1.7 mph/0% grade if patient did not reach THR at peak exercise and regadenoson was administered SPECT •Rest protocol •Dual head detector camera •Gated: Yes •AC:no	Hemodynamic changes •All Patients:14% •Age <65 yrs:16%(p<0.05) >65 yrs:10%(p<0.05) Chest Discomfort •All Patients:13% -No:14%(p<0.05) -Non-Insulin dependent:11%(p<0.05) -Insulin dependent:7%(p<0.05) •CAD -No:11% -Yes:15% Dizziness •All Patients:7% GI symptoms •All Patients:1.9% •Gender -Female:4%(p<0.05)	N/A	
						SOB •Gender -Female:18%(p<0.01) -Male:9%(p<0.01) BMI<30 vs. ≥30 =NS		

MI: Myocardial Infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PET: Positron emission tomography; PTCA: Percutaneous transluminal coronary angioplasty; HTN: hypertension; NR: Not reported; CAD: Coronary artery disease: AC: Attenuation correction; ETT: exercise treadmill testing; SPECT: Single photon emission computed tomography; THR: Threshold heart rate; COPD: Chronic obstructive pulmonary disease; SOB: Shortness of breath; N/A: Not applicable; N: Number; FDG: Fluorodeoxyglucose; SD: Standard deviation; LVEF: Left ventricular ejection fraction; BMI: Body mass index; GI: Gastrointestinal

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Mixed Risk								
de Souza Leão Lima (2008) Design: Randomized trial (multiple tested groups) Setting: Single center	SPECT • Tc-99m sestamibi • Dobutamine Accelerated protocol: Incremental dosing of dobutamine to 40 µg/kg/min, followed by atropine Conventional protocol: Injection of atropine following initial dose of dobutamine (10 µg/kg/min)	Total n = 168 Accelerated SPECT n=84 Male: 50% (42/84) HTN: 53.6% Diabetes: 22.6% Conventional SPECT n=84 Male: 54.8% (46/84) HTN: 51.2% Diabetes: 20.2%	Risk: NR Symptomatic: NR Suspected CAD: 67% Known CAD: 33%	Inclusion: • Symptoms or abnormal ECG in patients w/suspected CAD • Symptoms in patients w/known CAD • Contraindications for vasodilator stress testing Exclusion: • Asthma/COPD • Complete LBBB • Atrial fibrillation	SPECT: • 2-day stress/rest protocol • Dual-head camera (Millenium VG) • Gating: NR • AC: NR • Visual and semi-quantitative scoring (AHA)	Dobutamine dose • Accelerated SPECT: 31.8 ± 6.8 µg/kg/min • Conventional SPECT: 38.5 ± 6.8 µg/kg/min • p<0.001 Patients w/ventricular premature complexes • Accelerated SPECT: 14 (16.7%) • Conventional SPECT: 33 (39.3%) • p=0.002 Overall adverse events • Accelerated SPECT: 29 (34.5%) • Conventional SPECT: 46 (54.8%) • p=0.01	Fair Randomization method NR SPECT images interpreted by observers blinded to protocol assignment	Hemodynamic data, ECG response and perfusion scores for protocols reported
Hilleman DE (1997) Design: Retrospective Cohort (Multiple tested groups) Setting: Outpatient	Adverse effects in Adenosine Dipyridamole	Total n=249 Adenosine SPECT n=166 Mean (SD) age: 67.0 (10.7) Female: 58% Mean weight (kg): 79.9 (18.5) HTN: 58% Dipyridamole SPECT n=83 Mean (SD) age: 67.0 (11.4) Female: 55% Mean weight (kg): 81.9 (22.6) HTN: 60%	Total n=249 Adenosine SPECT: n=166 Mean (SD) age: 67.0 (10.7) Male: 42% Mean weight (kg): 79.9 (18.5) HTN: 58% Dipyridamole SPECT: n=83 Mean (SD) age: 67.0 (11.4) Male: 45% Mean weight (kg): 81.9 (22.6) HTN: 60%	Inclusion: •Patients referred for SPECT from Jan 1994 to March 1995 for CAD evaluation	SPECT •Single day protocol •Thallium-201 •Bruce or Naughton protocol for exercise stress •Gating: NR •AC: no	Average no. of side effects per patient Adenosine:1.64±1.32 Dipyridamole:1.36±1.23 p=0.10 No. of patients reporting: ≥1 side effect Adenosine:81% Dipyridamole:76% p=0.37 Late-onset side effects Adenosine:0% Dipyridamole:50% p<0.0001 Prolonged duration side effects(≥5 mins) Adenosine:0% Dipyridamole:46% p<0.001 Side effects requiring medical intervention Adenosine:5% Dipyridamole:24%; p<0.001	Fair Control for confounding NR	

SPECT: Single photon emission computed tomography; SD: Standard deviation; HTN: hypertension; ICA: Invasive coronary angiography; CAD: Coronary artery disease; NR: Not reported; AC: Attenuation correction; ECG:Electrocardiogram; N: Number

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Dakik HA (1996) Design: Series Setting: Laboratory	No comparator, side effects during dobutamine infusion studied	n=1012 Mean age:63±15 yrs Male:51%	Risk: NR Symptomatic:NR Prior MI: 28%	NR	•Tc- 99m sestamibi or 201-Thallium •Dobutamine	<u>Adverse effects:</u> Chest pain: 30.5% Headache:13.6% Dyspnea: 12.2% Flushing: 10.3% Palpitation:9.7% Nausea:8% Tremors:1.1% Nonsustained ventricular tachycardia:4.2% Premature ventricular complexes:12% Premature atrial complexes:1.6% Afib: 1.1% Atrial flutter:0.1%	N/A	
Kabasakal L (1996) Design: Retrospective cohort (single group, single test) Setting: NR	No comparator, Endogastric Bile reflux from the medical records of a cohort was studied	n= 1405 Male: 52% Age range: 19-89 Prior gastric surgery:0.9%	Risk: NR Symptoms: NR Known or suspected CAD	NR	<u>SPECT</u> •One day stress/rest protocol •99m Tc Sestamibi •Dipyridamole or dobutamine •Treadmill stress •Gamma camera •Gating and AC: NR	Endogastric bile reflux(EGBR): 8.3% EGBR with treadmill test: 5.5%(P<0.005 vs. pharmacological stress) EGBR frequency women:7%(p=NS) EGBR more frequent in age>40 vs. age<40 (p<0.01)	N/A	
Chaptini N (2010) Design: Prospective Cohort (Descriptive study, one cohort divided into two based on stress type) Setting: Outpatient (Mobile nuclear cardiology lab)	Adverse effects of stress MPI	n= 1260 Mean age: 58.6±4.2 Males:57.1% Mean BMI:29.2±1.8 Diabetes:24% HTN:56.1% Family history CAD:33.7%	Risk: NR Symptomatic: 73% Suspected CAD:91.3%	<u>Inclusion:</u> •All patients referred to nuclear cardiology lab by their PCP between August 2007 and September 2009	<u>SPECT</u> •Single day protocol •Tc-99m Tetrofosmin or Sestamibi •Bruce protocol for exercise stress •Adenosine •Gating: NR •AC: NR	<u>Exercise Stress</u> n= 947 Chest pain: 3% (95%CI=±1.1) Dyspnea: 15.9%(95%CI=±2.33) Flushing: 0 Wheezing: 0 Nausea, vomiting: 0 <u>Pharmacologic Stress</u> n=319 Chest pain: 26%(95%CI=±4.8) Dyspnea: 18.8%(95%CI=±4.3) Flushing: 33.2%(95%CI=±5.2) Wheezing: 1.2%(95%CI=±1.2) Nausea,vomiting: 7.2%(95%CI=±2.8) (p values NR)	N/A	

CAD: Coronary artery disease; AC: Attenuation correction; EGBR: Endogastric bile reflux; NS: Not significant; NR: Not reported; N/A: Not applicable; HTN: Hypertension; MPI: Myocardial perfusion imaging; PCP: Primary care physician; CI: Confidence interval; N: Number

Table C6. Risks of cardiac nuclear imaging tests, by population

Author (Year) Study Design Study Setting	Intervention Comparator	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes Assessed Main Findings	Quality Evaluation	Notes
Wright DJ (2001) Design: Randomized cross-over (multiple testing groups) Setting: NR	Adverse effects of Adenosine SPECT Dobutamine SPECT Arbutamine SPECT	n=40	Risk: NR Symptomatic: NR Patients under investigation for suspected CAD	Inclusion •Unable to exercise Exclusion •Previous revasc •MI within 8 weeks •UA in 14 days •LBBB •Second or third degree heart block •Diabetes •Allergy to adenosine, dobutamine or arbutamine •Significant valvular heart disease •SBP<100 mmHg, poorly controlled HTN	SPECT •99mTc-tetrofosmin •Dual-headed gamma camera	Incidence of side effects Chest pain Adenosine:46% Dobutamine:62% Arbutamine:77%(p<0.05 vs. adenosine) Palpitations Adenosine:25%(p<0.05 vs. dobutamine) Dobutamine:69% Arbutamine:54%(p<0.05 vs. adenosine) Abnormal taste Adenosine:54%(p<0.05 vs.dobutamine) Dobutamine:23% Arbutamine:23%(p<0.05 vs. adenosine) Flushing Adenosine:68% Dobutamine:54% Arbutamine:35%(p<0.05 vs.adenosine)	N/A	
Treuth MG (2001) Design: Randomized Trial Setting: Nuclear Cardiology Laboratory	3 min adenosine infusion 6 min adenosine infusion	N=599 Males=52% 3 min adenosine infusion group Mean age:65.4±11.7 Diabetes:32% HTN:65% Obesity:13% Family History:36% 6 min adenosine infusion group Mean age:66.2±10.9 Diabetes:31% HTN:65% Obesity:15% Family History:33%	Risk: NR Symptomatic: NR Prior MI 3 min: 21% 6-min: 25%	Exclusion • High-grade AV block •COPD or asthma	SPECT •99m Tc Sestamibi or Th-201 •Single day protocol	3-min group Flushing:41% Headache:23% Neck pain:19% Nausea:6% Av-block:5% Dyspnea, chest pain, throat pain, abdominal pain and dizziness NS	Poor High drop-out rate (31%) Control for confounding NR	

HTN: Hypertension; NR: Not reported; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disorder; SPECT: Single photon emission computed tomography; NS: Not significant; N: Number; N/A: Not applicable

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Symptomatic, Low-Intermediate Risk							
Shaw LJ (2011) Design: Randomized trial Setting: 43 cardiology practices	ETT Exercise SPECT Follow-up: 24 months	Total n = 772 ETT: n=388 Median age: 63 (60,69) Female: 100% BMI: 27.4 (24.2, 30.9) Family history: 47.3% Current/past smoker: 48.8% HTN: 55.2% Hyperlipidemia: 50.0% Diabetes: 12.6% Exercise SPECT: n=384 Median age: 62 (58,68) Female: 100% BMI: 27.4 (24.6, 31.8) Family history: 45.8% Current/past smoker: 42.4% HTN: 52.0% Hyperlipidemia: 53.7% Diabetes: 14.2%	Pre-test likelihood by ACC/AHA guidelines Intermediate risk: 100% Symptomatic :100% Suspected CAD: 100%	Inclusion: • Typical/atypical chest pain or ischemic equivalents (e.g. dyspnea) • Interpretable baseline ECG • Age ≥40 years or postmenopausal • Capable of performing ≥5 metabolic equivalents on the DASI questionnaire • Intermediate pre-test likelihood of CAD Exclusion: • Known CAD (history of MI or catheterization w/a >50% lesion in ≥1 coronary artery • ≤5 metabolic equivalents on the DASI • Pregnant/nursing women • Nuclear medicine study w/in 10 days of study • Electrocardiographic abnormalities such as LBBB, ventricular pacemaker	ETT: • Standard or modified Bruce protocol • Blood pressure, 12-lead ECG monitoring SPECT: • Tc-99m tetrofosmin • Thallium • No pharmacologic stressor used • 3 potential protocols w/Tc-99m: 1) Rest-thallium/stress-tetrofosmin 2) 2-day tetrofosmin 3) 1-day tetrofosmin (rest/stress sequence) • Gating: when possible • AC: advised, but optional • Visual scoring w/aid of quantitative programs	Index testing: [Mean(SD)] • ETT: $154.28 ($30.42) • SPECT: $495.24 ($8.54) • p<0.001 Follow-up testing: [Mean(SD)] • ETT: $179.97 ($413.64) • SPECT: $144.77 ($407.75) • p=0.0008 Total costs: [Mean(SD)] • ETT: $337.80 ($416.26) • SPECT: $643.24 ($411.51) • p<0.001	Costs estimated from applying a nationwide reimbursement rate from CMS outpatient PC Pricer database of HCPCs w/inflation adjustment for medical care component of CPI and 3%/year discount rate ECG/SPECT interpretation conducted by site investigators
				• Significant valvular disease (e.g. severe aortic stenosis) • Uncontrolled HTN (>210/110 mmHg) • Hypotension (<90/60 mmHg) • History of heart failure • LVEF <50% • Patients receiving digoxin therapy			

ETT: Exercise treadmill testing; SPECT: Single photon emission computed tomography; BMI: Body mass index; HTN: Hypertension; CAD: Coronary artery disease; DASI: Duke activity status index; ECG: Electrocardiogram; CMS: Centers for Medicare and Medicaid Services; AC: Attenuation correction; LVEF: Left ventricular ejection fraction; N: Number; MI: Myocardial infarction; LBBB: Left bundle branch block; SD: Standard deviation; CPI: Consumer Price Index; HCPC: Healthcare Common Procedure Code

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Min JK (2008) Design: Retrospective matched cohort Setting: 2 regional health plans	CCTA SPECT	Total n=8,235 (1,647 CCTA, 6,588 SPECT) Each CCTA patient matched to 4 SPECT patients on clinical and demographic criteria Mean (SD) age: 50.5 (12.7) Male: 31.2% Diabetes: 10.5% HTN: 5.2%	Low risk (based on claims-based "cardiac risk score" Symptomatic: NR No CAD: 100%	Inclusion: •Received CCTA or SPECT from 2002-2005 •Test received was initial diagnostic test •Without prior evidence of CAD Exclusion: •Not continuously enrolled in health plan for 1 year prior and 1 year following initial test •Unmatched patients	N/A	Unadjusted downstream costs (mean per patient): 1 month: •CCTA: $1,572 •SPECT: $2,531 •p<0.0001 6 months: •CCTA: $3,052 •SPECT: $4,082 •p<0.001 12 months: •CCTA: $3,542 •SPECT: $4,605 •p<0.0001	Costs did not include costs of initial test 12-month costs were also compared for entire unmatched population (n=39,174); costs were ~$1,800 higher for SPECT on average Median effective radiation dose (at baseline) CCTA: 6mSv SPECT: 13.3mSv Downstream radiation MPS vs. CCTA;p=NS Cumulative radiation exposure CCTA:7.3 MPS:13.3; (P<0.0001)
Iwata K (2013) Design: Decision analysis Setting: Outpatient	SPECT MRI Time horizon: NR	Base case: adult outpatients with stable chest pain and normal or equivocal stress EKG	Assumed pretest likelihood of CAD: 35% Symptomatic: NR Known vs. Suspected: NR	N/A	Assumed test performance of MRI (vs. ICA): Sensitivity: 75% Specificity: 89% Assumed test performance of SPECT (vs. ICA): Sensitivity: 64% Specificity: 83% No differences in MACE event rates or mortality assumed	Clinical Effectiveness: •MRI: 91.2% •SPECT: 87.3% Diagnostic Cost per Patient: •MRI: 181,275 JPY ($2,308 US) •SPECT: 225,463 JPY ($2,870 US) Diagnostic + Treatment Cost per Patient: •MRI: 644,239 JPY ($8,202 US) •SPECT: 626,296 JPY ($7,973 US) Cost per Successful Outcome: •MRI: 4,661 JPY ($59 US) (based on Dx+Rx costs only)	Assumed treatment limited to PCI All lesions confirmed by ICA assumed to receive PCI Costs included those of diagnostic tests, ICA, and elective or emergent PCI

SPECT: Single photon emission computed tomography; HTN: Hypertension; CAD: Coronary artery disease; NR: Not reported; N/A: Not applicable; CCTA: Coronary computed tomography angiography; N: Number; SD: Standard deviation; MPS: Myocardial perfusion SPECT; NS: Not significant; MACE: Major adverse cardiovascular events; JPY: Japanese yen; DX: Diagnosis; RX: Prescription; MRI: Magnetic resonance imaging; EKG: Electrocardiogram; ICA: Invasive coronary angiography; PCI: Percutaneous coronary intervention

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Bedetti G (2008) Design: Decision analysis Setting: Emergency department	Strategies evaluated: 1. Troponin 1 or T-->ICA 2. ETT-->ICA 3. Exercise ECHO-->ICA 4. Rx ECHO-->ICA 5. Exercise SPECT-->ICA 6. ICA Alone Time horizon: diagnostic phase only	1000 hypothetical patients with acute chest pain	Risk: Low-to-intermediate (assumed) Symptomatic: 100% Known vs. Suspected: NR	N/A	Sensitivity: Troponin 1 or T: 24% ETT: 43% Exercise ECHO: 85% Rx ECHO: 85% Exercise SPECT: 86% Specificity: Troponin 1 or T: 99% ETT: 95% Exercise ECHO: 95% Rx ECHO: 96% Exercise SPECT: 90% Feasibility: Troponin 1 or T: NR ETT: 79% Exercise ECHO: NR Rx ECHO: 97% Exercise SPECT: 97%	Total Strategy Costs for 1000 patients (incl. radiation-related): Troponin 1: $1,704,161 Troponin T: $1,814,482 ETT: $1,608,327 Exercise ECHO: $750,282 Rx ECHO: $525,945 Exercise SPECT: $1,460,505 ICA Alone: $5,609,733 Cost per Correctly Identified Patient: Troponin 1: $2,051 Troponin T: $2,086 ETT: $1,890 Exercise ECHO: $803 Rx ECHO: $533 Exercise SPECT: $1,634 ICA Alone: $29,999	Costs included direct costs of tests, false negatives, radiation-induced cancers Radiation-related costs for downstream ICA following troponin, ETT, or ECHO testing not considered
Hachamovitch R (2002) Design: Retrospective cohort (Single group, single test) Setting: Urban, university-affiliated community hospital	SPECT Follow-up: mean (SD) of 1.6 (0.5) years	Total n=3,058 SPECT MPS: n=3,058 Mean (SD) age: 61 (12) Female: 35% Mean (SD) # cardiac risk factors: 1.3 (1.0)	Mean (SD) likelihood of CAD: Pre-ETT: 35% (25%) Post-ETT: 31% (33%) Symptomatic: NR Known vs. Suspected: NR	Inclusion: • Exercise SPECT between 1991-1993 Exclusion: • Abnormal resting EKG • Revascularization within 60 days after SPECT • Lost to follow-up	SPECT MPS: •Thallium-201 (rest) •Tc-99m sestamibi (stress) •Exercise-based •Rest-stress protocol •AC: None •Gating: NR •Scoring: Semiquantitative SSS and SRS	Cost per MACE event detected with added SPECT data: •Low risk (pre-ETT): $211,470 •Low risk (post-ETT): $147,000 •Intermediate risk (post-ETT): $25,134 Cost per appropriate risk reclassification: •All patients: $18,190 •Intermediate-to-high risk (post-ETT): $5,417	Event rates determined via survival analysis to account for differential follow-up

SPECT: Single photon emission computed tomography; NR: Not reported; EKG: Electrocardiogram; CAD: Coronary artery disease; ICA: Invasive coronary angiography; ETT: Exercise treadmill test; ECHO: Echocardiography; N/A: Not applicable; SD: Standard deviation; MPS: Myocardial perfusion SPECT; SRS: Summed rest score; SSS: Summed stress score; RX: Prescription; MACE: Major adverse cardiovascular events; AC: Attenuation correction

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Mishra JP (1998) Design: Retrospective Cohort (Multiple tested groups) Setting: NR	Group 1 (ICA as screening test) Group 2 (SPECT as screening test)	Group 1 (ICA as screening test) n= 4,572 Mean age:59±11 Males:62% HTN:44% Diabetes:14% Single-vessel Disease:28% Multi-vessel disease:72% Group 2 (SPECT as screening test) n=2,022 Mean age:57±12 (p>0.001) Males:55% (p>0.005) HTN:42% (p=NS) Diabetes:10% (p=NS) Single-vessel Disease:28%	Pryor et al method of risk assessment Intermediate risk:100% Symptomatic: 100% Suspected CAD: 100%	Inclusion •Evaluated for chest pain symptoms due to CAD Exclusion •Previous revasc. •Cardiomyopathy •Valvular heart disease	SPECT •Thallium-201 •Bruce protocol for stress test •Gating: NR •AC: no	Assuming Medicare reimbursement of SPECT=$840 and ICA=$2800; Total cost per patient in group 1: $2,800 US Total cost per patient in group 2: $1,380 US Cost Savings in Group 2= 1,420/patient	

SPECT: Single photon emission computed tomography; NR: Not reported; CAD: Coronary artery disease; ICA: Invasive coronary angiography; HTN: Hypertension; N: Number; AC: Attenuation correction

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Symptomatic, High Risk							
Sabharwal NK (2007) Design: Randomized trial Setting: Hospital chest pain clinic	ETT Exercise SPECT Follow-up: 24 months	Total n = 457 ETT: n=207 Mean (SD) age: 58.9 (11.4) Male: 57.5% Family history: 46.3% HTN: 46.3% Mean (SD) BMI: 27.6 (4.6) Diabetes: 14.5% Exercise SPECT: n=250 Mean (SD) age: 59.7 (12.2) Male: 55.6% Family history: 43.3% HTN: 53.2% Mean (SD) BMI: 26.9 (4.5) Diabetes: 19.2%	Pre-test likelihood by ACC/AHA guidelines Pretest likelihood: • Low: 11% • Intermediate: 71% • High: 18% Symptomatic: 100% Suspected CAD: 100%	Inclusion: • Age >25 • Suspected CAD Exclusion: • Acute coronary syndromes • Known CAD • Pregnant or lactating • Abnormal resting EKG	ETT: • Symptom-limited or modified Bruce protocol • Blood pressure, 12-lead EKG monitoring Exercise SPECT: • Tc-99m sestamibi •Exercise, dipyridamole, or dobutamine stress •Stress/rest protocol (if stress test abnormal) • EKG gating: Yes • AC: NR • Semiquantitative visual interpretation	Mean Cost "to Diagnosis": Based on Hospital Costs: • ETT: £460 ($707 US) • Exercise SPECT: £507 ($779 US) • p=0.062 Based on NHS Cost Estimates: • ETT: £810 ($1,244 US) • Exercise SPECT: £484 ($743 US) • p<0.001 Similar findings in subgroup of patients achieving ≥85% of maximum predicted heart rate on exercise	Hospital and NHS costs significantly lower in ETT arm among patients with low pretest likelihood of CAD 31% of patients did not achieve MPHR Equivocal Treadmill test ETT:39% SPECT:14%
Hayashino Y (2006) Design: Decision analysis(Multiple groups) Setting: Outpatient screening	Strategies evaluated: 1. No screening 2. ETT 3. Exercise ECHO 4. Exercise SPECT Time horizon: lifetime	Base case: hypothetical cohort of asymptomatic men with Type 2 diabetes, age 60, who smoke	High-risk (100%)	N/A	Assumed prevalence of asymptomatic ischemic CAD: Base case: 32% Lower: 22% Upper: 42% Incidence of CAD per yr: Base case: 1.4% Lower: 1.0% Upper: 1.8%	Lifetime Costs, QALYs: •No screening: $135,332, 11.24 •ETT: $138,986, 11.36 •Exercise ECHO: $139,917, 11.39 •Exercise SPECT: $140,699, 11.39 Cost per QALY gained: •ETT (vs. no screening): $31,400 •Exercise ECHO (vs. ETT): $31,500 •Exercise SPECT (vs. ECHO): $326,000	Costs included direct medical and "opportunity" costs (e.g., patient travel, waiting time) Cost-effectiveness ratios for any repeat screening strategy (using ECHO as an example) >$1 million per QALY gained for intervals of 3, 5, and 10 years

SPECT: Single photon emission computed tomography; ETT: Exercise treadmill testing; NR: Not reported; CAD: Coronary artery disease; PCI: percutaneous coronary intervention; HTN: Hypertension; N: Number; AC: Attenuation correction; SD: Standard deviation; ACC: American College of Cardiology; AHA: American Heart Association; EKG: Electrocardiogram; N/A: Not applicable; MPHR: Maximum predicted heart rate; QALY: Quality-adjusted life-year; BMI: Body mass index; NHS: National Health Services

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Known CAD							
Holmberg MJ (1997) Design: Retrospective case control(Multiple groups) Setting: university hospital outpatient metabolic imaging	Dipyridamole Adenosine (Controls): Matched by age, body weight, sex, previous MI, previous CABG or PCI, ratio 2:1	Total n=108 Adenosine PET: n=72 Mean (SD) age: 58.9 (10.9) Male: 79% Mean weight (kg): 75.7 (18.3) HTN: 43% Dipyridamole PET: n=36 Mean (SD) age: 59.3 (12.2) Male: 79% Mean weight (kg): 76.9 (17.1) HTN: 44%	Risk: NR Symptoms:NR All patients with history of CAD (prior MI, revascularization, or both)	Inclusion: •Referred for cardiac PET between 1993-1996 •Diagnostic angiography within prior 8 weeks •Known CAD	Cardiac PET: •Rest-stress perfusion imaging •N-ammonia •Adenosine or dipyridamole •FDG rest metabolic scan •AC: Yes •Scoring: Qualitative Follow-up: Outpatient encounter only	Cost Comparison (mean, SD): Adenosine: •Acquisition: $186 ($30)* •Administration: $20 ($6) •Monitoring: $339 ($43)* •AE Mgmt: $18 ($41)* •Follow-up: $16 ($45)* •TOTAL: $577 ($123)* Dipyridamole: •Acquisition: $120 ($24)* •Administration: $24 ($12) •Monitoring: $491 ($104)* •AE Mgmt: $54 ($82)* •Follow-up: $39 ($133)* •TOTAL: $728 ($234)* Median costs adjusted for diagnostic accuracy: •Adenosine: $672* •Dipyridamole: $928* *p<.05 for between-group comparison	Cost analysis performed for vasodilators only, PET test costs not considered
Siegrist PT (2008) Design: Prospective Cohort (Same cohort, multiple strategies tested) Setting: NR	Patient management before PET results Patient management after PET results	n= 100 Mean age:60.9±12 Male:72% Previous CABG:44% Previous PCI:45%	Risk: NR Symptomatic: NR Known CAD:79% Suspected CAD:8% Suspected small-vessel disease: 13%	Inclusion •Patients enrolled to rule out or evaluate CAD between Jan 2004 and Feb 2005	PET •Discovery LS PET CT scanner (GE Healthcare) •13 N-Ammonia •Adenosine •Gating: NR •AC: yes	Difference in cost after PET results % patients referred for ICA Before PET results:62% After:0% Cost difference:-149,420€ (-$194,246 US) % patients referred forPCI: Before PET:6% After:20% Cost difference:48,860€ ($63,518 US) % patients referred for PET Before PET:0 After:87 Cost difference:82,650€ ($107,445 US) Total difference:-17,910€ ($23,283 US)	

CAD: Coronary artery disease; PCI: percutaneous coronary intervention; HTN: Hypertension; PET: Positron emission tomography; MI: Myocardial Infarction; CABG: Coronary artery bypass grafting; FDG: Fluorodeoxyglucose; NR: Not reported; N: Number; AC: Attenuation correction; AE: Adverse event; SD: Standard deviation; ICA: Invasive coronary angiography

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Mixed Risk							
Min JK (2012) Design: Randomized trial (multiple tested groups) Setting: 2 outpatient cardiology clinics	CCTA SPECT Follow-up: Mean (SD) of 55 (34) days	Total n = 180 CCTA: n=91 Mean (SD) age: 55.9 (10) Male: 58% Family history: 41% HTN: 62% Diabetes: 23% SPECT: n=89 Mean (SD) age: 58.9 (9.5) Male: 43% Family history: 48% HTN: 59% Diabetes: 21%	Risk: NR Symptomatic:100% Suspected CAD: 100%	Inclusion: • Age 40 or older • No known history of CAD • Stable chest pain • Suspected CAD • Determination by referring physician of need for non-invasive imaging Exclusion: • Suspected acute coronary syndrome • Life expectancy <2 years • Pregnant/nursing women • Allergy to contrast agent • Serum creatinine ≥1.7 mg/dL • Irregular heart rhythm • Heart rate ≥100 beat/min • Systolic BP ≤90 mm Hg • Contraindication to beta-blockers or nitroglycerin • Class I ACC/AHA indication for urgent or emergent ICA	CCTA: • 64-slice scanner • 64 X 0.625 mm of collimation • Tube voltage 120 mV • EKG gating: Yes • Interpretation: Semiquantitative SPECT: • Tc-99m sestamibi or Thallium 201 • Exercise or adenosine stress • EKG gating: Yes • AC: NR • Visual scoring according to ASNC reporting guidelines	Mean downstream costs per patient: <u>Abnormal test result:</u> • CCTA: $380 • SPECT: $441 • p=0.30 <u>Normal test result:</u> • CCTA: $235 • SPECT: $422 • p=0.03 Total costs per patient (including initial test): • CCTA: $781 • SPECT: $1,215 • p<0.001	All analyses adjusted for differences in age and sex

SPECT: Single photon emission computed tomography; CABG: Coronary artery bypass grafting; NR: Not reported; CAD: Coronary artery disease; AC: Attenuation correction; ICA: Invasive coronary angiography; CCTA: Coronary computed tomography angiography; N: Number; SD: Standard deviation; BP: Blood pressure; ACC: American College of Cardiology; AHA: American Heart Association; EKG: Electrocardiogram; ASNC: American Society of Nuclear

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Sharples L (2007) Design: Randomized Trial (Multiple tested groups) Setting: Tertiary cardiothoracic referral center	SPECT MRI stress-ECHO ICA (controls) Follow up:18 months	<u>SPECT</u> Mean age:62.1±9.5 Males:70% Mean BMI:27.3±4.3 Family history of CAD:8% Treated HTN: 59% <u>MRI</u> Mean age:62.2±9 Males:68% Mean BMI:28±4.4 Family history of CAD:9% Treated HTN: 51% <u>stress-ECHO</u> Mean age:61.9±9.9 Males:71% Mean BMI:27.9±4.2 Family history of CAD:10% Treated HTN: 57% <u>ICA</u> Mean age:60.7±9.1 Males:67% Mean BMI:27.6±4.2 Family history of CAD:27% Treated HTN:53%	Pryor Risk assessment High: 69% in all groups Symptomatic:% NR Known CAD: NR	<u>Inclusion:</u> •Known or suspected CAD, referred for ICA and ETT results indicate referral to ICA Exclusion: •MI<3 months •Functional test <12 months •UA or urgent revascularization •Physically unable to perform ETT •Not available by telephone	SPECT •Two day rest-stress protocol •Adenosine •Gating: When available •AC: NR MRI •1.5-t MAGNET SYSTEM (Signa CV/I, GE Medical Systems) •Stress-rest protocol •Adenosine stress-ECHO •Standard protocol increasing dobutamine dose at 3 minutes duration •Intravenous ultrasound contrast(microspheres) ICA •50% stenosis in left main stem or 70% stenosis in any other major vessel=significant CAD •Seldingers technique; femoral route	Mean total additional costs compared to ICA (95% CI) SPECT:£415(-£310 to £1084) $630(-$470 to $1645) MRI: £426(-£247 to £1088) $647(-$375 to $1652) stress-ECHO: £821(£10 to £1715) $1246($29 to $2604) Difference in QALY between groups<0.04 over 18 months	NHS 2005-06 costs used for overall analysis

SPECT: Single photon emission computed tomography; MRI: Magnetic resonance imaging; NR: Not reported; CAD: Coronary artery disease; ICA: Invasive coronary angiography; ETT: Exercise treadmill test; ECHO: Echocardiography; HTN: Hypertension; MI: Myocardial infarction; AC: Attenuation correction; BMI: Body mass index; QALY: Quality-adjusted life-year; NHS: National Health Services; UA: Unstable angina

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Merhige M (2007) Design: Prospective Cohort (Multiple tested groups) Setting: Outpatient	SPECT PET Follow-up:1year	<u>SPECT</u> n=102 Median age:62±11 Male:54% Known CAD:44% Suspected CAD:56% <u>PET</u> n=2,159 Median age:66±8 Male:54% Known CAD:49% Suspected CAD:51%	Risk: NR Symptomatic: NR Known CAD: SPECT: 44% PET: 49%	<u>Inclusion:</u> •Patients with moderate pre-test likelihood of CAD in PET arm <u>Exclusion:</u> •Patients with pretest likelihood <0.11 or >0.70 (CADENZA)	<u>PET</u> •HZL/R camera •Rubidium-82 •Gating: NR •AC: Yes <u>SPECT</u> •99.Tc-Sestamibi •One-day or two-day protocol •Dual-headed gamma camera(CardiaL;ElScint) •Gating: Yes •AC: NR	Diagnostic costs: SPECT:$2,506 PET:$2,475 Therapeutic cost SPECT:$3431 PET:$1635 Total cost SPECT:$5937 PET:$4110 52% savings in revasc costs with PET vs. SPECT 30% reduction in CAD management costs in absence of adverse clinical outcomes	
Hilleman DE (1997) Design: Retrospective Cohort (Multiple tested groups) Setting: Outpatient	Adenosine SPECT Dipyridamole SPECT Follow-up: 5 minutes after end of drug infusion or until end of monitoring	Total n=249 Adenosine SPECT: n=166 Mean (SD) age: 67.0 (10.7) Male: 42% Mean weight (kg): 79.9 (18.5) HTN: 58% Dipyridamole SPECT: n=83 Mean (SD) age: 67.0 (11.4) Male: 45% Mean weight (kg): 81.9 (22.6) HTN: 60%	Risk: NR Symptomatic: NR Previous MI Adenosine: 39% Dipyridamole: 29%	<u>Inclusion:</u> •Referred for Thallium SPECT between 1994-1995 •Unable to exercise	No protocol details provided Follow-up: Outpatient encounter only	Cost Comparison (mean, SD): Adenosine: •Acquisition: $184 ($30)* •Administration: $19 ($5)* •Monitoring: $151 ($21)* •AE Mgmt: $13 ($40)* •Follow-up: $12 ($90) •TOTAL: $380 ($128)* Dipyridamole: •Acquisition: $128 ($31)* •Administration: $26 ($7)* •Monitoring: $247 ($67)* •AE Mgmt: $50 ($79)* •Follow-up: $34 ($145) •TOTAL: $486 ($230)* *p<.05 for between-group comparison	Cost analysis performed for vasodilators only, SPECT test costs not considered

PET: Positron emission tomography; CAD: Coronary artery disease; NR: Not reported; AC: Attenuation correction; SPECT: Single photon emission computed tomography; N: Number; AE: Adverse event; HTN: Hypertension

Table C7. Economic evaluation of myocardial perfusion imaging, by population

Author (Year) Study Design Study Setting	Intervention Comparator Follow-up	Sample Size and Patient Characteristics	Risk Assessment Level of Risk	Inclusion/Exclusion Criteria	Testing Protocol	Outcomes	Notes
Muzzarelli S (2010) Design: Retrospective Cohort (same cohort, multiple tests) Setting: NR	ETT SPECT Follow-up: NR	Total n=955 Mean (SD) age: 61 (11) Male: 70% Mean (SD) BMI: 27.5 (4.6) Known CAD: 43% Diabetes: 23% HTN: 63% Family History: 32%	Duke treadmill test Risk: Low: 4% Intermediate: 86% High: 10% Symptomatic Typical Angina:23% Atypical Angina: 32% Dyspnea: 34% Known CAD:43%	Inclusion: • Referred for SPECT • Able to undergo exercise stress Exclusion: • ST-segment depression ≥1 mm on baseline EKG • Left bundle branch block on baseline EKG	ETT: • Standard or modified Bruce protocol • Blood pressure, 12-lead ECG monitoring • Risk stratification based on Duke score SPECT: • Tc-99m sestamibi • Thallium-201 • No pharmacologic stressor used • Rest/stress protocol • EKG gating: Yes • AC: No • Semiquantitative visual interpretation	Diagnostic costs (based on hypothetical risk stratification from test results): • ETT only: 615€ ($798 US) • SPECT only: 1,299€ ($1,686 US) • Combined (ETT first, SPECT for abnormal ETT): 598€ ($776 US) • p=0.02	Cost estimates include those of ETT, SPECT, and ICA for hypothetically referred patients Hypothetical referral rates were 27% for ETT only, 13% for SPECT only, and 12% for combined strategy
Risk NR							
Tardif JC (2002) Design: Prospective cohort(Multiple tested groups) Setting: Multicenter evaluation	Stress ECHO Stress SPECT Both tests Follow-up: 3 months	Total n=59 Mean (SD) age: 57.1 (10.1) Male: 57.8% Mean (SD) wt: 86.5 (18.2) kg Employed: 44.1%	Risk: NR Symptoms: Typical Angina: 13.6% Atypical Chest pain: 28.8% Non specific chest pain: 11.9% Suspected CAD: 100%	Risk: Low-to-intermediate (assumed) Symptomatic: 100% Known vs. Suspected: NR	Stress ECHO: • Harmonic imaging with our without contrast Stress SPECT: • Details NR Both Tests: • Dobutamine, dipyridamole, or exercise (Bruce protocol) stress	Total 3-month diagnostic costs: • ECHO: 444 Can ($285 US) • SPECT: 615 Can ($395 US) • p= 0.001 Cost per successful diagnosis • ECHO: 476 Can ($306 US) • SPECT: 637 Can ($409 US) •p=NR Total pathway cost reduced by 56 can when results of both tests available	Both ECHO and SPECT performed in all patients Costs of planned treatment estimated by separate investigators based on single test results Revised treatment plan created with both test results and costs adjusted Equivocal contrast ECHO:7%

ETT: Exercise treadmill testing; SPECT: Single photon emission computed tomography; SD: Standard deviation; NR: Not reported; CAD: Coronary artery disease; HTN: Hypertension; EKG: Electrocardiogram; AC: Attenuation correction; ICA: Invasive coronary angiography; N: Number

APPENDIX D

Figure D1. Structure of decision tree using ETT→ECHO as an example. Decision Model for 2-test strategy evaluating short-term diagnostic and economic outcomes of myocardial perfusion testing.

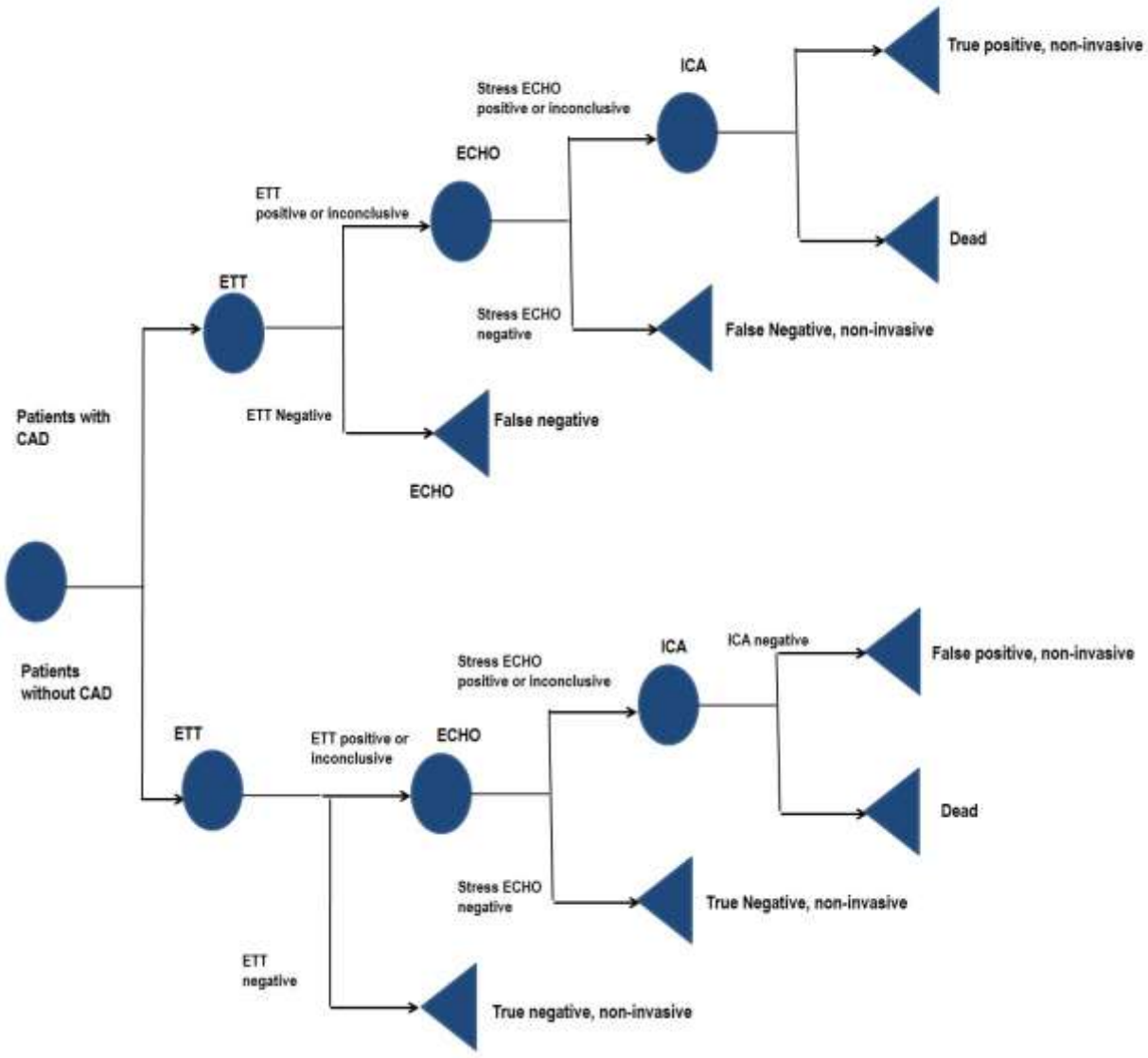
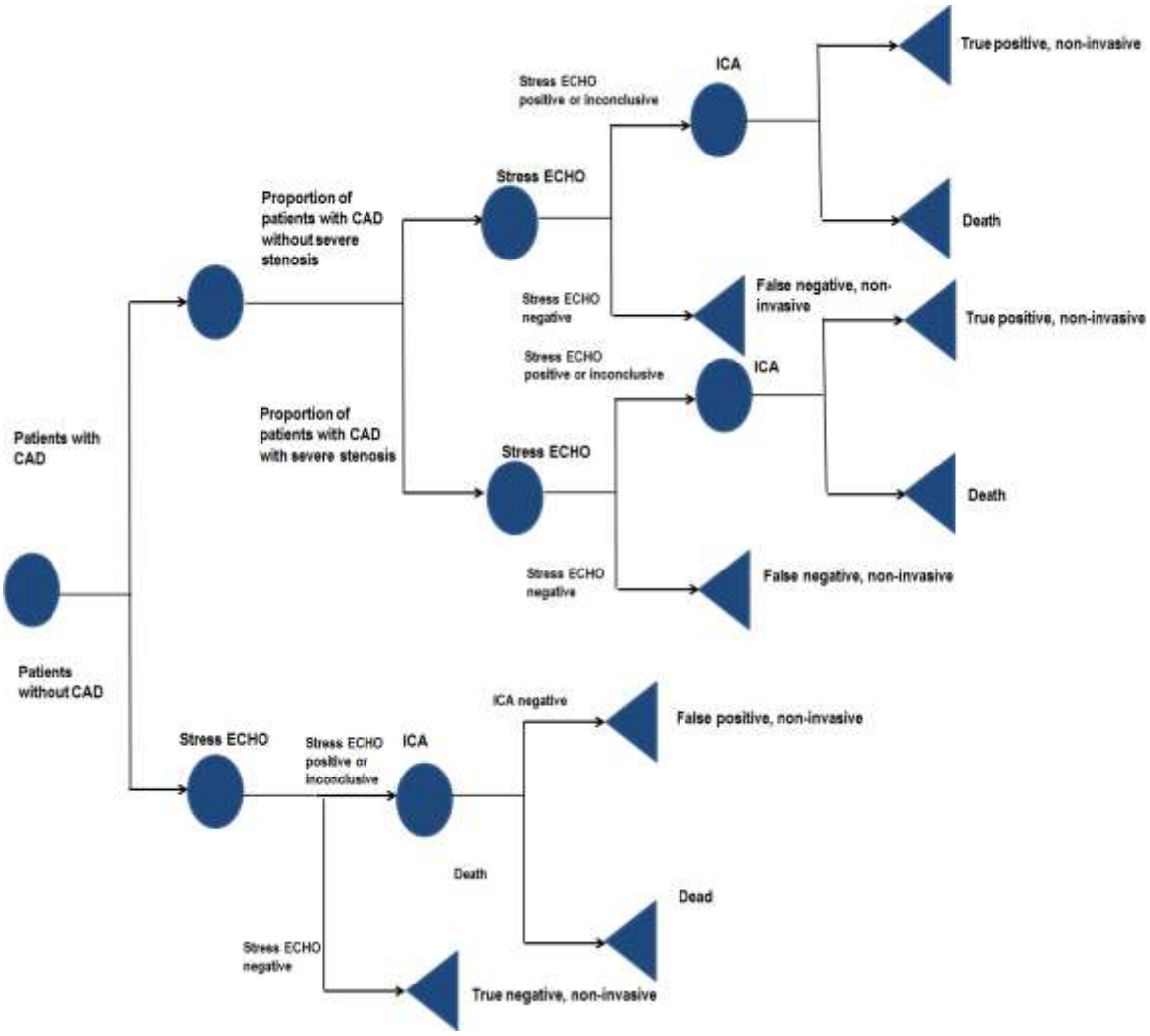


Figure D2. Structure of decision tree using single test stress-ECHO as an example but incorporating disease severity.



APPENDIX E

Table E1: Results from patients with high risk (50%) of CAD – sensitivity and specificity values for ECHO and SPECT from Fleischmann 1998* (instead of de Jong 2012).

	ECHO	ETT	SPECT	PET	ETT ---> ECHO	ETT ---> SPECT	ETT ---> PET
True Positive, non-invasive	427	365	435	464	314	319	340
False Positive, non-invasive	140	194	192	111	55	75	43
True Negative, non-invasive	359	305	307	389	445	425	457
False Negative, non-invasive	70	133	62	34	185	179	158
Referred for angiography	571	562	630	578	370	396	386
Angiography negative results	140	194	192	111	55	75	43
Angiography related deaths	3	3	4	3	2	2	2
Exposed to radiation	571	562	1000	1000	370	562	562
Incidental findings requiring f/u	57	0	8	8	32	5	5
Total costs/patient [excluding all f/u costs, $)	2438	1883	3237	5074	1688	2114	3204

* ECHO: Sensitivity 0.85, Specificity 0.77; SPECT: Sensitivity 0.87, Specificity 0.64 versus ECHO: Sensitivity 0.87, Specificity 0.72; SPECT: Sensitivity 0.83, Specificity 0.77 in de Jong et al 2012

Table E2: Results from patients with high risk (50%) of CAD – sensitivity and specificity values for SPECT from Parker 2012* (instead of de Jong 2012).

	ECHO	ETT	SPECT	PET	ETT ---> ECHO	ETT ---> SPECT	ETT ---> PET
True Positive, non-invasive	437	365	441	464	320	324	340
False Positive, non-invasive	163	194	134	111	64	53	43
True Negative, non-invasive	336	305	365	389	436	447	457
False Negative, non-invasive	61	133	56	34	178	174	158
Referred for angiography	603	562	579	578	386	379	386
Angiography negative results	163	194	134	111	64	53	43
Angiography related deaths	4	3	3	3	2	2	2
Exposed to radiation	603	562	1000	1000	386	562	562
Incidental findings requiring f/u	57	0	8	8	32	5	5
Total costs/patient [excluding all f/u costs, $)	2538	1883	3080	5074	1737	2059	3204

* SPECT: Sensitivity 0.88, Specificity 0.76 versus Sensitivity 0.83, Specificity 0.77 in de Jong et al 2012

Table E3: Results from patients with very low risk (2%) of CAD

	ECHO	ETT	SPECT	PET	ETT ---> ECHO	ETT ---> SPECT	ETT ---> PET
True Positive, non-invasive	17	15	17	19	13	12	14
False Positive, non-invasive	319	381	254	217	125	99	85
True Negative, non-invasive	659	597	724	762	854	880	895
False Negative, non-invasive	2	5	3	1	7	8	6
Referred for angiography	339	398	272	237	138	112	99
Angiography negative results	319	381	254	217	126	100	85
Angiography related deaths	2	2	2	1	1	1	1
Exposed to radiation	339	398	1000	1000	138	398	398
Incidental findings requiring f/u	57	0	8	8	22	3	3
Total costs/patient [excluding all f/u costs, $)	1730	1380	2143	4032	865	1030	1784

Table E4: Results from Patients with High Risk (50%) of CAD – Sensitivity and Specificity values for SPECT and PET from ICER Functional meta-analysis*

	ECHO	ETT	SPECT	PET	ETT ---> ECHO	ETT ---> SPECT	ETT ---> PET
True Positive, non-invasive			371	420		272	308
False Positive, non-invasive			120	83		47	32
True Negative, non-invasive			379	417		453	467
False Negative, non-invasive			127	77		226	190
Referred for angiography			494	506		321	343
Angiography negative results			120	83		47	33
Angiography related deaths			3	3		2	2
Exposed to radiation			1000	1000		562	562
Incidental findings requiring f/u			8	8		5	5
Total costs/patient [excluding all f/u costs, $)			2820	4855		1884	3073

* SPECT: Sensitivity 0.74, Specificity 0.79 versus Sensitivity 0.83, Specificity 0.77 in basecase; PET: Sensitivity 0.84, Specificity 0.87 versus Sensitivity 0.93, Specificity 0.81 in basecase

Table E5: Results from probabilistic sensitivity analysis for patients with high risk (50%) of CAD

	ECHO	ETT	SPECT	PET	ETT ---> ECHO	ETT ---> SPECT	ETT ---> PET
True Positive, non-invasive	437	365	416	464	320	305	340
False Positive, non-invasive	163	194	132	111	63	51	43
True Negative, non-invasive	336	305	367	388	436	448	456
False Negative, non-invasive	61	133	81	70	202	181	158
Referred for angiography	603	561	551	579	386	359	386
Angiography negative results	163	194	132	111	64	52	44
Angiography related deaths	4	3	3	3	2	2	2
Exposed to radiation	603	561	1000	1000	386	561	561
Incidental findings requiring f/u	56	0	8	8	32	5	5
Total costs/patient [excluding all f/u costs, $)	2542	1887	3001	5083	1739	2002	3207